

# Guidelines for Phase I clinical trials *2018 edition*

# Preface

The first edition of these ABPI guidelines was published in 1970<sup>1</sup>. Since then the guidelines were revisited on a few occasions and in 2007, underwent a major revision taking into account the many changes that had taken place in the two decades since the 1988 edition.

However, developments in the regulatory arena are moving at a fast pace and a considerable amount of what previously constituted guidance has now become a legal requirement. Moreover, an impressive range of guidance documents dealing with various aspects of conducting clinical trials has been published by Health Authorities and other stakeholder organisations around the world in recent years. However, many readers still feel the benefit of a comprehensive, largely jargon-free document that outlines the framework within which Phase I research is conducted and provides pointers for further, more in-depth reading. In 2012, the ABPI therefore released an updated version of the 2007 edition. This edition was extremely well received and became a useful guide not only to sponsors and investigators but also to ethics committees and trial subjects, read by people well beyond the borders of the United Kingdom.

This new 2018 edition reflects the current EU legislation for the performance of Phase I clinical research as set down in the EU Clinical Trials Directive<sup>2</sup>. Until the Clinical Trials Regulation EU No 536/2014 becomes applicable, all clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive.

In addition to regulatory changes, this new edition now also incorporates the previous ABPI First in Human Studies guidelines with the aim of compiling all the different aspects of conducting Clinical Pharmacology Phase I trials into a single document.

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# 1 Developing a new medicine

The pharmaceutical industry is the main sponsor of new medicines research in the UK. Sponsors have to demonstrate the safety, quality and efficacy of a potential new medicine – called an investigational medicinal product (IMP)<sup>3</sup> – through a series of rigorous trials in humans in order to obtain a licence, so that doctors can give the medicine to patients.

However, before an IMP can be given to humans, sponsors must first test it thoroughly in animals and/or *in vitro/ex vivo* models. The main aims of these pre-clinical studies are:

- to find out the effects of the IMP on body systems (pharmacodynamics) and thereby to provide translational information supporting the hypothesis that the IMP could be effective in humans
- to study the blood levels of the IMP and how it is absorbed, distributed, metabolised and eliminated after dosing (pharmacokinetics)
- to find out if some of the doses of the IMP, up to many times higher than those intended for use in humans, are toxic to animals<sup>4</sup> and if so, to identify the target organs and the margin of safety in terms of (a) the no-observed-adverse-effect dose level (NOAEL) relative to body weight and (b) IMP exposure - the concentration of IMP in the bloodstream over a dosing interval, e.g. 24 hours (toxicokinetics)<sup>5</sup>, and
- to make a formulation of the IMP, extravascular or intravascular, suitable for early studies in humans.

After the pre-clinical studies, there are four phases of trials in humans, which in practice often overlap and which can be sub-divided. Phases I to III are done before a licence is granted and Phase IV is done after authorisation to market the drug. The phases are different in terms of the number and types of subjects studied, and the questions asked, as outlined in table 1.

Clinical trials of an IMP that do not benefit subjects – whether they are healthy subjects or patient subjects – may be called Phase II or non-therapeutic trials<sup>3</sup>. The premises where these trials are conducted are often (but not always) called Phase I units, or simply units. People who take part in clinical trials are called subjects<sup>3</sup>: healthy subjects when they are truly healthy, and patient subjects when they have the disease for which the IMP is being developed.

**Table 1. Clinical trial phases and questions they intend to answer**

Phase	Number and type of subject	Questions
I	Approx. 50–200 <b>subjects (either healthy or patients)</b> who are not expected to benefit from the IMP (except for life-threatening diseases)	<ul style="list-style-type: none"> <li>• Is the IMP safe in humans?</li> <li>• What does the body do to the IMP? (pharmacokinetics)</li> <li>• What does the IMP do to the body? (pharmacodynamics)</li> <li>• Might the IMP work in patients?</li> </ul>
II	Approx. 100–400 <b>patients with the target disease</b>	<ul style="list-style-type: none"> <li>• Is the IMP safe in humans?</li> <li>• What does the body do to the IMP? (pharmacokinetics)</li> <li>• What does the IMP do to the body? (pharmacodynamics)</li> <li>• Might the IMP work in patients?</li> </ul>
III	Approx. 1000–5000 <b>patients with the target disease</b>	<ul style="list-style-type: none"> <li>• Is the IMP really safe in patients?</li> <li>• Does the IMP really work in patients?</li> <li>• Does the IMP seem to work better than other medicines for the same disease?</li> </ul>
IV	Many thousands or millions <b>patients with the target disease</b>	<ul style="list-style-type: none"> <li>• Just how safe is the new medicine? (pharmacovigilance)</li> <li>• Does the medicine work in the real world? (real world data collected to demonstrate value)</li> <li>• How does the new medicine compare with similar medicines?</li> </ul>

The numbers in the table are indicative only and can vary

Phases are also often subdivided. A small-scale, exploratory efficacy study in a limited number of patients may be referred to as ‘Phase IIa’. In contrast, slightly larger trials that test the efficacy of a compound at different doses (‘dose-range finding’ studies) might be designated ‘Phase IIb’.

Phases I to III can take up to 10 years or more for a successful IMP. However, many IMPs are withdrawn from development<sup>6</sup>, mainly because:

- they are not well-tolerated or safe enough in humans, or
- their pharmacokinetic (PK) or pharmacodynamic (PD) profile in humans is disappointing, or
- they do not work or do not work well enough in patients with the target disease.

In reviews of the historical clinical success of IMPs<sup>7,8</sup>, only 60–70% progressed from Phase I to II, and a mere 10–15% became a marketed product. Phase I trials can identify IMPs with potential for success as well as excluding failures and thereby preventing unnecessary exposure of the IMP to many more subjects.

The past decade has seen the introduction of exploratory studies that are performed prior to the traditional Phase I Single-Dose Escalation (also referred to as Single Ascending Dose, or Single Rising Dose). These studies allow early exploration of potential drugs in humans, to evaluate, for example, human PK, and therapeutic target relevance to disease. These studies involve exposure of a limited number of subjects to a much-reduced dose (also referred to as a micro-dose) of a novel compound, have no therapeutic or diagnostic intent, and are not intended to examine the maximum tolerated dose. Guidance on this type of study can be obtained from the Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA)<sup>4</sup>.

While the categorisation of human drug development trials into distinct phases implies chronology, in practice there can be considerable overlap. A range of Phase I studies are performed when the IMP is already in a more advanced stage of development.



A Phase I study (exploratory or clinical pharmacology studies) is typically defined as non-therapeutic. This contrasts with Phase II, III or IV clinical studies which are therapeutic trials.

The primary parameters tested in Phase I studies (which can involve single or multiple doses of the IMP) are:

- safety and tolerability
- PK
- PD (including biomarkers).

Traditionally there was a range of distinct Phase I studies, each of which was designed to address a particular question or set of questions. In recent years, there has been a trend to combine these studies into larger multi-part studies, where the data in the early parts influences the doses and procedures in the later parts.

The building blocks of a Phase I programme are discussed below.

### 1.1 First-in-Human trial (Phase I exploratory trial)

First-in-Human (FIH) clinical trials are part of the exploratory phase of drug development and represent a significant milestone in the clinical development of new medicines. At this stage, only pre-clinical data are available to guide dose selection, population, study design, safety monitoring and appropriate expertise, and all of these are critical to maximise the safety of the study subjects and the quality of the data<sup>4</sup>. The new compound is first tested in cohorts of healthy volunteers or – with increasing frequency – patients at increasing single doses (single ascending dose study).

There has been intense focus on the risks of FIH clinical trials since the TeGenero TGN1412 incident in 2006 and more recently since the Bial incident in 2015, and much has been published on the evidence and recommendations<sup>10–14</sup>. The EMA's Guideline on strategies to identify and mitigate risks for FIH and early clinical trials with IMPs provides an excellent overview of points to consider. However, vigilance is still warranted in view of the fatal serious adverse event in the recent trial BIA-102474-101 clinical trial<sup>14</sup>.

The following are key aspects for a FIH study:

- choice of study population
- study design considerations
- selection of an appropriate study site and principal investigator (PI)
- formulation and site pharmacy considerations
- starting dose, and dose escalation decisions
- informed consent considerations.

These aspects are all considered in Section 6 on risk management.

### 1.2 Subsequent parts/studies (clinical pharmacology trials)

After the FIH trial, the next study (or next study part if included in a single protocol) is usually an exploration of multiple ascending doses, which is still exploratory.

Examples of other clinical pharmacology Phase I trials (which contribute to further characterise the IMP) are listed below:

- the effects of potential influences, such as food, gender, age and genetic/ethnicity differences, on the PK of the IMP
- the relationship between dose or blood concentration of the IMP and the body's response – for example, by measuring biomarkers<sup>16</sup> or using challenge agents (Appendix 2)
- the possible interaction of the IMP with marketed medicines (Drug-Drug Interactions)
- the absorption, distribution, metabolism and elimination (ADME) of a radiolabelled IMP
- the bioavailability of the IMP (how much of the IMP is taken up by the body) or bioequivalence (how similar does a generic compound behave to the branded original brand)<sup>17</sup>, and
- the effect of the IMP on the electrical activity in the heart as measured by the QT interval of the electrocardiogram (ECG)<sup>18</sup>.

As stated above there is an increasing tendency for sponsors to combine the first single ascending dose and multiple ascending dose trials of an IMP, and even include the effect of food or age, so that the FIH trial is actually a 'bundle' of parts, the first part of which is the FIH evaluation.

Some of these trials, such as the drug-drug interaction trials, ADME and QT-interval trials, may be conducted during any stage of development of an IMP.

While it is customary to refer to PK studies as 'Phase I', this is not very helpful and might lead to confusion. In general, these studies form part of a set of trials classified as 'clinical pharmacology studies', expanding from FIH through to registration (and beyond). Together they make up Section 2.7.2 of the common technical document (which is a set of specifications-for-application dossier for the registration of medicines across Europe, Japan and the United States).

## 2 Regulations

**In recent years, many changes have been made to the regulatory aspects of clinical trials. Most changes stem from the introduction of Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and the European Clinical Trials Directive, which is based on GCP and GMP.**

All clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive until the new Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable. Both the Directive and Regulation apply to all phases, including Phase I, regardless of the trial population.

The new Clinical Trials legislation, which was adopted on 16 April 2014 and entered into force on 16 June 2014, has taken the legal form of a Regulation.

The main regulatory documents are:

- International Conference on Harmonisation (ICH) Guideline for GCP<sup>19</sup>
- European Union (EU) Clinical Trials Directive 2001/20/EC<sup>20</sup>
- ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals<sup>4</sup>
- ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals<sup>21</sup>
- ICH S9 Nonclinical evaluation for anticancer pharmaceuticals<sup>22</sup>
- GMP for Medicinal Products. EudraLex Vol. 423, 24 and Annexes, especially Annexes 1, 13 and 16<sup>25-27</sup>
- Directive 2003/94/EC on GMP for Medicinal Products and IMPs<sup>28</sup>

- Directive 2005/28/EC on GCP<sup>29</sup>
- Governance Arrangements for Research Ethics Committees (GAfREC)<sup>30</sup>
- Standard Operating Procedures (SOP) for Research Ethics Committees (REC)<sup>31</sup>
- European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), July 2017. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational Medicinal Products [EMA/CHMP/SWP/28367/07 Rev.1]<sup>15</sup>.

The Clinical Trials Directive was implemented in the UK through the Clinical Trials Regulations<sup>3</sup> in May 2004 (also known as Statutory Instrument (SI) 2004/1031). The SI has since been amended on an annual basis. The Directive's aims were:

- to simplify and harmonise clinical trials across Europe
- to give better protection to subjects who take part in clinical trials, and
- to enforce by law the principles of GCP and GMP.

In addition to the Clinical Trials Directive, the European Commission has published a set of guidelines covering a range of clinical trial aspects (EudraLex, Vol. 10<sup>23</sup>). EudraLex is a 10-volume body of regulations and guidelines governing medicinal products in the European Union.

The scope of the Clinical Trials Directive is wide; it covers all commercial and academic clinical trials of IMPs and marketed medicines, apart from trials using marketed medicines prescribed in the intended way.

The types of IMP are:

- chemical entities
- biotechnology products
- cell therapy products
- gene therapy products
- plasma-derived products
- other extractive products
- immunological products, such as vaccines, allergens and immune sera
- herbal products
- homeopathic products
- radiopharmaceutical products.

In addition, a placebo, or a marketed product used or assembled in a way different from the approved form, is an IMP when used as a comparator.

## Clinical trial transparency

### EU-CTR

When the European Union Clinical Trial Regulation becomes applicable, all information stored in the database is to be **publicly available**, unless exempted under the Regulation to protect:

- personal data
- commercially confidential information, in particular the marketing-authorisation status of the medicine, unless there is an overriding public interest
- confidential communication between Member States in the preparation of their assessment
- supervision of clinical trials by Member States.

The EMA has added two sets of requirements to the functional specifications for **applying the exceptions**:

- features to support making information public
- disclosure rules describing the practical implementation of the transparency rules.

Details can be found on EMA's Clinical Trial Regulation website<sup>32</sup>.

## Health Research Authority

HRA requirements on clinical trials transparency can be accessed via the HRA website<sup>33</sup>.

In particular, HRA transparency requirements for Phase I studies<sup>34</sup> can be accessed via the HRA website regarding information on Phase I trial registration and publication of research summaries and the HRA Registration Deferral Policy and Procedure including for the publication of research summaries<sup>35</sup>.

## ABPI Code of Practice

Following a change to the ABPI Code of Practice in 2012<sup>36</sup>, companies must disclose details of clinical trials in accordance with the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases<sup>37</sup> and the Joint Position on the Publication of Clinical Trial Results in the Scientific Literature<sup>38</sup>.

Companies are obliged to:

- publicly register trials within 21 days of initiation of patient enrolment; and
- post results within 12 months of completed trials for medicines licensed for use and commercially available in at least one country (completed on or after 1 May 2011 for non-interventional studies).

## 3 MHRA

### 3.1 Clinical Trial Authorisation (CTA) application

The sponsor of a clinical trial of an IMP must submit a CTA application to the Medicines and Healthcare products Regulatory Agency (MHRA). There is an algorithm for deciding if a trial requires a CTA<sup>39</sup>. The MHRA must respond to a valid application within the period specified in the Directive. However, applications for Phase I studies in healthy and patient subjects are usually assessed and processed within 14 days.

The MHRA reviews trials of higher-risk IMPs, or those with greater elements of uncertainty (see Section 5), differently from trials of other IMPs. They seek advice for FIH trials of higher-risk IMPs from the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG) of the Commission on Human Medicines (CHM) before approval is given. The Expert Advisory Group was established after the TeGenero incident. Sponsors can seek advice from the MHRA about whether their IMP is higher risk, once they have submitted a summary of the nature of the IMP, its target or mechanism of action, and the relevance of the animal model(s).

### 3.2 Protocol amendments

The MHRA reviews any substantial protocol amendments. Some amendments for Phase I trials need a rapid review to keep the study running smoothly. However, the MHRA has no formal procedure for expedited review, although the aim is to assess and process these amendments within 14 days, as for the initial applications. Therefore, whoever writes the protocol should include appropriate flexibility to try to allow for unforeseen findings and thereby avoid protocol amendments.

### 3.3 Inspections

The MHRA (or in fact any other Health Authority) can inspect any site involved in a clinical trial. The inspectors assess GCP and GMP compliance separately. Inspections are compulsory, system- or trial-specific, and may be announced or unannounced. Units should be prepared for an inspection at any time.

The inspector prepares for an inspection by reviewing the sponsor's CTA application and requesting and reviewing documents from the site, such as SOP, details of computer

systems critical for GCP, charts of how the staff are organised, and contracts. GMP inspections may be prepared for differently to GCP inspections. More information on GMP inspections can be found on the MHRA's website<sup>40</sup>.

During the visit, the inspector starts by meeting key staff, and then interviews selected staff, inspects the facilities, and reviews relevant documents and records. The inspector gives verbal feedback to staff at the end of the visit.

After the visit, the inspector writes and circulates a report (urgent action may be required before this); requests and reviews the investigator's or site's responses to the findings (which are graded in the report); and makes conclusions and recommendations (this might include re-inspection or enforcement action).

In 2007 the MHRA introduced a scheme of voluntary accreditation, in particular for units conducting FIH trials. Under this scheme, units are inspected by the agency against sets of pre-defined criteria. While the scheme is still voluntary, it has found widespread acceptance and Phase I units are encouraged to apply for MHRA accreditation to demonstrate that they meet those criteria.

Detailed information about the scheme, including a Question & Answer document, can be found on the MHRA's website<sup>41</sup>.

### 3.4 Breaches of GCP or trial protocol

The sponsor or delegate must notify the MHRA within seven days of any serious breach of GCP or the protocol. A serious breach is one that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial, or
- the scientific value of the trial.

Sponsors and investigators should have a procedure in place to assess whether a deviation from the protocol or a failure to comply with the principles of GCP constitutes a serious breach. The sponsor has responsibility for assessing the impact of the breach on the scientific value of the trial. The MHRA offers guidance on identifying and notifying serious breaches, and the consequences.

## 4 Research Ethics Committee

Before starting a Phase I trial in healthy subjects or in patients, the investigator must obtain written approval of a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA).

Guidance on the process of applying for ethics approval, types of RECs, communications with RECs during a clinical

trial, and protocol amendments can be found on the website of the NHS Health Research Authority<sup>42</sup>.

## 5 Risk assessment

### 5.1 All IMPs

Subjects (healthy or patient) who volunteer for Phase I trials get no potential therapeutic benefit from the IMP, so the risk of harming the subjects must be minimal<sup>43</sup>. The risk must be assessed before each trial, especially during the transition from pre-clinical studies to the FIH trial, when uncertainty about tolerability and safety of the IMP is usually at its highest. The sponsor must have the pre-clinical data reviewed by people who have the appropriate technical, scientific and clinical expertise. At least one reviewer should be independent of the project. Sponsors who do not have the expertise themselves must use external advisers instead. All aspects of the IMP – such as its class, novelty, species specificity, mode of action, potency, dose- and concentration-response relationship for efficacy and toxicity, and route of administration – must be taken into account. Risk must be assessed on a case-by-case basis, and there is no simple formula. The seriousness of possible adverse reactions and the probability of them happening must both be considered.

### 5.2 Higher risk IMPs

The Department of Health Expert Scientific Group (ESG) on Phase One Clinical Trials Report<sup>10</sup> deemed some agents to have a 'higher potential for risk of harm to subjects during the first human exposures'. The group provided examples of factors that should trigger particular caution:

- any agent that might cause severe disturbance of vital body systems
- agents with agonistic or stimulatory action

- novel agents or mechanisms of action for which there is no prior experience
- species-specificity making pre-clinical risk assessment difficult or impossible
- high potency, e.g. compared with a natural ligand
- multifunctional agents, e.g. bivalent antibodies
- cell-associated targets
- targets that bypass normal control mechanisms
- immune system targets, and
- targets in systems with potential for large biological amplification *in vivo*.

Experimental and/or literature data should be taken into account when defining the degree of uncertainty of the IMP.

The EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products<sup>15</sup> provides advice on risk factors to consider in FIH trials, particularly but not exclusively around:

- mode of action
- nature of the target
- relevance of animal models.

### 5.3 Other factors

The risk assessment must also take into account other factors, such as the procedures and any non-IMP (Section 16) used in the trial, and whether the trial should be carried out in healthy subjects or patients.

## 6 Risk management

**Before every Phase I trial, as well as assessing risk and justifying that assessment, there must be a strategy for ensuring that any risk is minimised throughout the trial.**

Should potential investigators be concerned about the level of risk of the IMP, the sponsor must give them access to people with responsibility for the relevant pre-clinical work. Also, the sponsor's physician should liaise with the investigator. If investigators still have concerns about pre-clinical data, they should consult an independent adviser.

Assessment and management of risks should be documented (e.g. through a risk management plan).

The strategy for managing risk should consider all aspects of the trial.

### 6.1 Choice of population

The majority of Phase I clinical trials use healthy subjects. This approach has the advantage of speed of recruitment and ease of scheduling cohorts of subjects throughout the study. It also removes potential confounding factors such as concomitant medication and disease pathology when

reviewing adverse event and PK data. Healthy subjects may generally tolerate more intensive interventions and adverse effects than would be expected from a symptomatic patient.

Historically, the use of patients has been commonplace for oncology agents and agents with low therapeutic index intended for life-threatening conditions. However, use of patients in other FIH and Phase I studies is increasing. Certain study designs may include 'bridging' between healthy subjects and a patient population once the expected therapeutically relevant dose is achieved in the escalation paradigm. This allows a more time- and cost-efficient early evaluation of PK, PD and safety parameters at lower doses in healthy subjects to facilitate improved dose-selection and/or regime at higher doses in the target patient population, in whom more informative safety or PD data can be generated.

Some pros and cons of healthy subjects versus patients are detailed in table 2.



**Table 2. Selection of healthy subjects versus patients**

	Healthy subjects	Patients
<b>PROs</b>	<ul style="list-style-type: none"> <li>• Easier and quicker recruitment and management in the clinical unit, resulting in more efficient study</li> <li>• No confounding pathology or medications</li> <li>• Easier to obtain blood for full PK profile</li> <li>• Data may be useful for several indications</li> <li>• Wide choice of potential FIH sites and investigators</li> <li>• High internal validity</li> </ul>	<ul style="list-style-type: none"> <li>• PD/biomarker and surrogate data may only be obtainable in patients</li> <li>• Target-related safety may be tested</li> <li>• Possible benefit, especially at higher doses (oncology settings)</li> <li>• High external validity</li> </ul>
<b>CONs</b>	<ul style="list-style-type: none"> <li>• Often no or limited target-related PD/biomarker data obtainable</li> <li>• Often difficult to justify target availability in healthy subjects (but may be expressed at low levels)</li> <li>• Target-related safety may be different from patients (but off-target toxicity likely to be similar)</li> <li>• PK may be different from patients</li> <li>• No therapeutic benefit to subjects, only potential risks</li> <li>• Low external validity</li> </ul>	<ul style="list-style-type: none"> <li>• Recruitment and management often more difficult, resulting in less efficient study (e.g. extended timelines and higher costs)</li> <li>• Sites that have the patients may have no experience in FIH clinical trials or facilities for extended in-house monitoring</li> <li>• Concomitant disorders and medications confound interpretation of safety data</li> <li>• Greater variability in safety signals</li> <li>• Target-related safety may still be different in other indications</li> <li>• Single dose, or low doses, may not provide adequate therapeutic benefit to justify entering very ill patients into the study, and may preclude participation in subsequent trials</li> <li>• Potentially more difficult to obtain blood for PK (consider sparse sampling for population PK)</li> <li>• Ethical concerns around placebo use</li> </ul>

For all studies, the safety of subjects and the value of the information that is likely to be obtained must be considered, especially:

- a) the risks inherent in the type of medicinal product and its molecular target
- b) potential immediate and long-term toxicity predicted from non-clinical or literature information
- c) the presence of the target, key biomarker or a surrogate marker in healthy subjects or in patients only, and the possibility and impact of higher variability in patients versus lower external validity in healthy subjects.

For all subjects it is also important to confirm the medical history of the healthy subjects or patients prior to inclusion in a FIH clinical trial, usually by contacting the primary care physician.

## 6.2 Study design considerations

In choosing design options for Phase I and FIH clinical trials, it is important to consider:

- factors linked to the compound characteristics (e.g. level of risk, PK, PD, number of dose levels to investigate, etc.)
- factors linked to the timelines and site logistics (e.g. number of doses per subject, number of subjects to be dosed per day relative to capacity of the clinical research unit to handle unexpected adverse events (AEs), risk of dropouts with multi-period study, flexibility to changes in the study design as clinical data are generated, etc.).

For a FIH study, once the development team has agreed the compound's level of risk<sup>15</sup>, they should consider whether the FIH design would include use of sentinel subjects or not. The EMA advises that it is usually appropriate to design the administration of the first dose so that a single subject receives a single dose of the active IMP, with justification of the period of observation before the next subject receives a dose. This approach is expected for all single and multiple dosing cohorts, in order to reduce the risks associated with exposing all subjects in a cohort simultaneously. Should the sponsor consider that the level of risk of the compound does not warrant such a design, documented justification within the protocol will generally be expected. Naturally consensus in these discussions will include key staff from the research site staff.

There is no regulatory need for a strict double-blind design in FIH clinical trials, and adoption of a single-blind design may be considered; however, the teams should weigh the risk of resulting bias in decision-making and in the review process for dose-escalation decisions.

In general, many different study designs can be adopted; a few examples are given below.

a) In a **sequential group design (Table 3)**, each cohort is assigned only one dose of active drug and subjects within a cohort are randomly assigned to receive either active drug or placebo, e.g. six on active and two on placebo. Doses are escalated sequentially with each cohort. For six doses, this design would require approximately three times the number of subjects required for the crossover design. A parallel group design may be appropriate when the projected half-life of a compound or metabolite is longer than can be accommodated in an interlocking

cohort, crossover design. In addition, it may be used when there is a concern about exposing subjects to more than one dose of active drug, or for biologics where neutralising antibodies could be formed or when the sponsor wants to explore between-subject variability.

**Table 3. Sequential group design**

### Single ascending dose escalation in healthy subjects

(NOMINAL DOSES SHOWN, P = placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP

Periods	I	II	III	IV	V	VI
Cohort 1 (2 P, 6 IMP)	'A' mg					
Cohort 2 (2 P, 6 IMP)		'B' mg				
Cohort 3 (2 P, 6 IMP)			'C' mg			
Cohort 4 (2 P, 6 IMP)				'D' mg		
Cohort 5 (2 P, 6 IMP)					'E' mg	
' Cohort 6 (2 P, 6 IMP)						'F' mg

b. **Crossover designs** may be favoured over parallel designs because they allow more efficient use of subjects who serve as their own controls with respect to safety, PK and PD, thereby reducing possible variability. Both within-subject and between-subject dose escalation is evaluated, allowing estimation of within-subject PK variability for calculation of sample size in subsequent studies.

This design may be well suited to small chemical molecules with a short half-life and where the identified risks and the toxicology pre-clinical data support multiple drug exposures within a subject. In addition, the potential for PK and/or PD carryover, the limitations in the number of blood samples that can be collected, subject dropouts, and time dependence in drug clearance or metabolic profile should be considered. While a crossover design may be prohibitive for drugs with prolonged half-lives or PD effects, it may prove useful to evaluate the influence of food on PK.



**b1. Sequential crossover cohorts (Table 4):** Doses are escalated within a cohort. Every subject receives two to three ascending doses of the IMP plus a single dose of placebo (i.e. a 3- or 4-way crossover). Usually, within-subject dose increments will be small, but a wider dose range can still be studied. The dosing interval for an individual subject should initially be determined on the basis of predicted human PK and confirmed once human PK and/or PD effect data becomes available.

**Table 4. Sequential crossover study design (standard)**

Single ascending dose escalation in healthy subjects (NOMINAL DOSES SHOWN, P=placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP						
WEEKS (nominal)	0	3	6	9	12	15
Cohort 1 (2 P, 6 IMP)	'A' mg	'B' mg	'C' mg			
Cohort 2 (2 P, 6 IMP)				'D' mg	'E' mg	'F' mg

**Table 5. Crossover study design (interlocking/alternating cohorts)**

Single ascending dose escalation in healthy subjects (NOMINAL DOSES SHOWN, P=placebo, A to F are ascending active doses of IMP); in each cohort, 2 subjects receive P, 6 receive IMP						
WEEKS (nominal)	0	3	6	9	12	15
Cohort 1 (2 P, 6 IMP)	'A' mg		'C' mg		'E' mg	
Cohort 2 (2 P, 6 IMP)		'B' mg		'D' mg		'F' mg

**b2. Interlocking/alternating cohorts (Table 5):** This is an efficient design allowing for longer washout periods between subjects. This may reduce the risk of PD and/or PK carryover and thus may be suitable for a compound where the parent or an active metabolite has a moderately long half-life. However, dose increments in this design are often larger and the longer study participation time may increase subject dropouts.

In summary, the choice of design for FIH studies should be tailored to the needs of the specific compound and development programme. The main factors to consider when choosing the design concern the compound and the logistical aspects, as discussed above.

## 6.3 Starting dose – FIH trials

Previous guidance suggested that the starting dose of an IMP should be a small fraction – not more than 10% – of the predicted therapeutic dose.

The FDA Guidance<sup>44</sup> method of calculating the safe starting dose in man follows a stepwise process:

- convert the NOAEL from the toxicology studies to a human equivalent dose (HED) on the basis of body surface area
- select HED from the most appropriate species
- apply a safety factor (≥10-fold) to give a Maximum Recommended Starting Dose (MRSD)
- adjust the MRSD on the basis of the predicted pharmacological action of the IMP.

This method is simple and supported by a wealth of historical evidence. However, the emphasis is on selecting a dose with minimal risk of toxicity, based on the NOAEL, rather than selecting one with minimal pharmacological activity in humans. Also, the focus is on dose rather than exposure.

Following the recommendations of the ESG report<sup>10</sup>, the EMA Guideline on strategies to identify and mitigate risks for FIH trials and early clinical trials with Investigational Medicinal Products<sup>15</sup> advises the use of a different approach to calculate a safe starting dose for high-risk agents, based on the minimal anticipated biological effect level (MABEL)<sup>13, 45</sup>. This approach uses all relevant information, taking into account: novelty; potency; mechanism of action; degree of species-specificity; dose-response data from human and animal cells *in vitro*; dose- and concentration-response data from animals *in vivo*; PK and PK modelling; calculated target occupancy versus concentration; and concentration of the target or target cells in humans *in vivo*.

**If different methods result in different estimates**, the lowest value should be used and a margin of safety built into the actual starting dose. If the pre-clinical data are assumed

to be a poor guide to responses in humans, the calculated starting dose should be reduced, and the dose increased in smaller increments should a steep dose-response curve be expected. A detailed discussion of the MABEL approach can be found in a paper by Muller et al.<sup>45</sup>

### 6.4 Increasing the dose – single or multiple ascending dose trials

In an ascending dose trial the dose is often increased three- to five-fold at each increment at the lower doses and smaller increments around the expected therapeutic range. Increases in dose, and the magnitude of the increase, should be made only after carefully assessing all of the available data from previous doses. Serial measurements of the IMP in blood (PK data) during the trial allow increases in dose to be guided by exposure to the IMP<sup>10</sup>. As a general rule, the 'dose/toxicity' or dose/effect relationship observed in non-clinical studies, depending on which is steeper, should guide the dose increment between dose levels. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected.

Target saturation should be taken into account when appropriate, then the maximum exposure should consider when complete inhibition or activation of the target is achieved and no further therapeutic effect is to be expected by increasing the dose.

The sponsor must put in place agreements with the investigator and research site staff to review and discuss pre-clinical data, safety and tolerability data, and PK and PD data when available, throughout the ongoing clinical trial.

Under the MHRA Phase I Accreditation scheme, the site should have procedures in place for dose escalation<sup>41</sup>. Study protocols should clearly state how dose escalation decisions will be made, i.e. what data will be used to make decisions, what the permissible boundaries of those decisions are and who will make the decisions.

#### Dataset

The minimum dataset required to make a decision and the number of subjects required for this dataset should be decided in advance. It should comprise adverse events, safety assessments such as physical examination, ECG or cardiac monitoring (e.g. telemetry and Holter monitoring),

vital signs, and clinical laboratory parameters as well as PK and PD data where applicable.

These data should be documented and commented on in an interim report by the PI.

#### Boundaries

Stopping rules must be defined in the protocol including emerging clinical data and non-clinical data, at both cohort and subject level. It is useful to write the protocol with flexibility. Wording around the dose escalation design should be sufficiently flexible to allow for adjustments based on new data emerging from the study as outlined above. This will prevent unnecessary protocol amendments.

#### Decision makers

There should be prior agreement on the composition of the trial safety review committee making the dose escalation decisions. Apart from the PI, this should include representatives from both the sponsor and the trial site. Sponsors without a physician experienced in FIH studies should use an independent medical monitor. Consideration should also be given to including external experts.

#### Meetings and documentation

Dose escalation meetings should be scheduled in advance to take place after each dose level is completed (or the pre-specified minimal data cut-off has been achieved) and before escalation to the next dose level. Ad hoc meetings may be needed if emerging data require more immediate action, or if dosing dates change. Meeting attendance and dosing decisions should be minuted and communicated to the site pharmacy in a timely fashion.

#### PK (and PD) data

Normally an assay will be available and validated to permit rapid analysis of the PK samples from the FIH clinical trial, as it is generally expected that PK data will be available prior to the administration of the next planned dose. There are situations when PK data may not be available, for example after the first dose, and justification of dose escalation without PK data should be agreed between the sponsor and the PI in advance of the clinical trial and documented in the protocol. If an acceptable biomarker for PD activity is available, this may replace the need for PK data and/or complement those.

## 6.5 Administration of doses

The number of subjects dosed on any one occasion, and the interval between dosing individual subjects and cohorts of subjects, whether it is single dose or multiple doses, will depend on the IMP, its route of administration, and the type of trial. For example, a sentinel approach, with only one subject given an active IMP and another one given a placebo, is likely to be recommended for the very first administration of a higher-risk IMP. In contrast, if the IMP is of low risk, with a mechanism which has already been tested in humans, cohorts of subjects may be dosed on the same day, and at shorter intervals, with the interval determined based on the required safety observations. The same applies for single ascending dose and/or multiple ascending dose parts of early Phase I trials.

The most flexible formulation is intravenous, as doses can be adjusted easily, and administration stopped during the infusion should significant adverse events occur. Slow intravenous infusions (time to be determined appropriately) using a controllable infusion pump are preferable to bolus administration for exploratory Phase I trials, unless there is a good reason otherwise. The protocol should include details for the rate and duration of infusion.

FIH clinical trials for orally administered compounds are often conducted using oral powder, which is then constituted for administration as either solution or a suspension, or powder-in-capsule, or a minimally formulated capsule fill, enabling dosing flexibility. If tablet formulations are used, the sponsor should plan maximum reasonable flexibility with the pharmaceutical development team, so that combinations of dose strengths can be used to span a wide dose-range and allow for unscheduled dose adjustments during the clinical trial.

## 6.6 Facilities and staff

FIH trials of an IMP are regarded as higher risk than later Phase I trials. However, the risk during transition from pre-clinical studies to the very FIH trial may be no higher than it is during other transition trials, such as from single to multiple doses, from young to elderly subjects, and from administration of the IMP alone to giving it with established medicines during interaction trials. Sponsors must place their trials of an IMP – especially a FIH trial and other transition trials – in Phase I units, including their own, whose staff, premises and facilities match the level of risk of the IMP. Investigators must not take on trials of an IMP for which

they do not have adequate experience or training.

The PI and unit staff responsible for the care of subjects in FIH clinical trials should always be appropriately qualified and experienced. In the UK, to act as a PI for a FIH Trial, a PI has to meet specific training and experience requirements, which are described in the MHRA Phase I voluntary Accreditation Scheme<sup>41</sup>. The sponsor should ensure that the investigator knows enough about the agent, its target, mechanism of action and potential adverse events to be in a position to manage the informed consent process with the subject, and to make informed clinical judgments during the study. The investigator must also understand the intricacies of executing FIH trials, including the potential need to adjust doses during the study as human data become available.

The investigator must assess the risk of harm, by reviewing the protocol, investigator's brochure, IMP dossier, CTA application and, as required by the Declaration of Helsinki<sup>46</sup>, any relevant medical and scientific literature. In addition, the investigator must weigh the foreseeable risks and inconveniences against the expected benefits for the individual subject, and for future subjects with the target disease. Finally, the investigator must explain and justify any risks in the information leaflet for trial subjects and in the REC application.

Appendix 1 of the MHRA's Phase I accreditation scheme requirements document<sup>47</sup> lists a range of standards relating to facilities, staff and procedures that are expected to be met by clinical research units conducting Phase I studies in the UK. These standards serve as guidance even for units that opt not to apply for accreditation.

The sponsor should conduct a site evaluation to consider the site's capabilities to meet the specific demands of a particular protocol such as appropriate medical governance, drug-specific biomarker methodologies or sample acquisition/analysis, the ability to recruit study participants, and pharmacy capabilities.

FIH clinical trials of IMPs with identified factors of risk should be conducted in research units with sufficient expertise and know-how and which, in the UK, have been awarded the MHRA Phase I Accreditation as they will have undergone a comprehensive scrutiny of their emergency equipment, procedures and training. However, this does not negate the importance of a site-evaluation by sponsor staff. It should be noted that the MHRA Phase I Accreditation is voluntary, i.e.

there is no mandatory requirement for it. Site assessment by the sponsor staff should include, but not be limited to:

- evaluation of the qualification, training and experience of the site staff (in particular the PI and sub PI if applicable) with FIH clinical trials and the ability to carry out appropriate safety monitoring
- the site's experience with IMPs of all levels of risk
- the site's process and experience with dose escalation decisions
- the site's facilities and ability for stabilising individuals in an acute emergency
- the site's ability to conduct resuscitation, the proximity to hospital, the access to Intensive Care Services, and ready availability of Intensive Care Unit facilities.

In FIH clinical trials where there is a predictable risk of certain types of severe adverse reaction, the sponsor should specifically address risk mitigation in the protocol, which should include considerations for treatment of such reactions. The sponsor and research site should ensure that any specific antidotes will be readily available, where they exist, as well as a clear plan of supportive treatment, including the pre-arranged contingency availability of intensive care facilities or specialty consultation.

The research site should assess the study-specific requirements for clinical cover and ensure that an appropriate level of staffing, with medical doctors during and after dosing, will be present.

For the FIH trials of IMPs other than those factors of risk, the sponsor should consider similar factors as previously discussed, on a case-by-case basis. As a minimum, the sponsor must assess facilities, training and experience of personnel, and the evidence that unit medical staff are appropriately qualified and trained in handling

emergency situations.

The sponsor should give consideration to the pharmacy licence, which is discussed in Section 11 below.

Finally, it is critical that subjects taking part in FIH clinical trials have not been recently exposed to other investigational products. Therefore, sites using web-based systems to monitor for 'over-volunteering'<sup>48</sup>, e.g. TOPS49, provide a valuable safeguard against the 'professional volunteer'. TOPS was run by an independent charity, but in April 2013, its function has come within the remit of Health Research Authority. It is a standard condition of ethical approval, as well as part of the MHRA accreditation scheme, that all Phase I studies using healthy subjects register research subjects onto TOPS and complete the record for each subject to specify whether they received a dose of the IMP.

## 6.7 Procedures

Non-invasive trial procedures should be used whenever possible. If invasive procedures – such as an arterial cannula, a biopsy or an endoscopy – are used, they must be conducted or supervised by someone skilled in the procedure.

## 7 Safety record of Phase I trials

Reviews of the safety of Phase I trials show that they have a good safety record<sup>50-52</sup>. Overall, the incidence of serious adverse events related to the IMP was about 0.02%. However, some accidents occurred in the recent past (2006 – Tegenero<sup>11,12</sup> and 2016 – Bial<sup>14,53</sup>) and these cases show that established medicines as well as IMPs have the potential to harm subjects in Phase I trials.

At one time, almost all IMPs were new chemical entities (NCE). Now, many are biological in nature (Section 14). Many biological IMPs – such as proteins<sup>54</sup>, cytokines<sup>55</sup>, and monoclonal antibodies<sup>56,57</sup> – have been tested safely in FIH trials in healthy subjects or in patients. However, compared with NCE, there is a paucity of data about their overall safety. Some reasons why biological IMPs, especially monoclonal antibodies, should be considered different from NCE are:

- Proteins can cause anaphylactic or infusion reactions.
- Even a single dose of a fully humanised protein can induce an immune response<sup>58</sup>.
- There is at least one report of a delayed hypersensitivity reaction<sup>59</sup> to re-challenge with a monoclonal antibody after a long period of non-exposure.
- Two monoclonal antibodies<sup>60,61</sup> in clinical use have caused progressive multifocal leukoencephalopathy (PML), a rare and usually fatal infection of the brain and spinal cord due to reactivation of a virus (JC polyoma) which most people carry. However, PML has almost always occurred in patients with profound immune dysfunction.
- TGN1412 – a monoclonal antibody that differs from those in clinical use in that it activates rather than blocks an immune response – caused a ‘cytokine storm’ and organ failure in all six previously healthy subjects who received it in a FIH trial<sup>11</sup>.

If the risk of giving a biological IMP to healthy subjects is more than minimal, patients with the target disease might be studied instead. However, the substitution of patients for healthy subjects must be carefully considered, especially if no potential benefit is expected to arise from participation in the study. Their condition might make patients more susceptible or less tolerant to unwanted effects from the investigational product. Also, the mass of tissue being targeted by the IMP may be much increased in patients compared with healthy subjects. A careful risk/benefit analysis should be performed before deciding on the appropriate study population. Properly validated biomarkers<sup>16</sup> may help monitoring potential risks.



## 8 Protocol

A clinical trial must be scientifically sound and described in a clear, detailed protocol<sup>23</sup>. It should contain, where appropriate, depending on the nature of the Phase I study:

- the pre-clinical information – such as pharmacology and toxicology – about the IMP
- the assessment of risk of harm from the IMP, trial procedures and any non-IMP (Section 16), the justification of that assessment, and how the risk will be kept minimal throughout the trial
- the methods of deciding: the first dose; the maximum dose; the increases in dose; the route of administration; the rate of administration of intravenous doses; the interval between dosing individual subjects; and the number of subjects to be dosed on any one occasion; the minimum set of data or subject numbers required for decision-making
- any assessment of dose- or concentration-response relations
- any pharmacy work needed to prepare doses of the IMP for administration (Sections 15 and 16)
- stopping or withdrawal criteria.

Often trials may require protocol amendments prior to their completion. There are two types of amendments: substantial and non-substantial. An amendment is substantial if it is likely to have a significant impact on:

- the safety or physical or mental integrity of the trial subjects
- the scientific value of the trial
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial.

The sponsor decides whether an amendment is substantial, and whether a substantial amendment requires MHRA and/or REC approval. Guidance on what constitutes a substantial amendment is provided in CT1 Vol 10, as well as the SOP of the Research Ethics Service (RES)<sup>31</sup>. The investigator and sponsor may implement a substantial amendment without REC and MHRA approval, respectively, if the change is an urgent safety measure to protect the

trial subjects. However, the investigator and sponsor must notify the REC and MHRA within three days afterwards - by telephone first and then by a written report.

In order to minimise the need for protocol amendments, it is advisable to apply an appropriate degree of flexibility when writing the protocol. For example, there should be scope to modify dose increments and frequency of blood sampling as safety and PK data become available. Additionally, the investigators should be able to use their clinical judgment to allow inclusion of subjects with minor out-of-range results of safety tests of blood and urine, and minor variants of the ECG.

The need for increased efficiency in the drug development process has seen the introduction of more flexible protocol designs (so-called 'adaptive designs'), where progression within a given study (e.g. subsequent doses in an ascending dose study) is not dictated by the protocol but by the results of individual trial sections. In such a setting, the protocol would simply provide the framework (e.g. minimum and maximum doses to be administered) but leave the exact dose at any given step and the number of steps to be determined during the trial depending on interim results, thus being 'adaptive' to the findings during the trial.

There are ongoing initiatives to standardise clinical trial protocols, such as the Common Protocol Template initiative by TransCelerate<sup>62</sup> which aims to increase consistency of protocol structure and language to simplify implementation.

## 9 Contracts

When entering into an agreement to conduct a trial, the sponsor must provide the investigator with copies of:

- the protocol
- an up-to-date investigator's brochure
- the IMP dossier
- the CTA application and approval letter
- indemnity and insurance (Section 19).

All of the above should be reviewed by the investigator.

If the investigator agrees to conduct the trial, there must be a written, dated and signed trial-specific contract between the sponsor and the investigator, and between the investigator and any subcontractors, which sets out the obligations of the parties for trial-related tasks and for financial matters. Examples of subcontractors are a laboratory and a commercial archivist. The protocol may serve as the basis of a contract. In order to protect the trial subjects, contracts must be in place before the start of the trial.

The contract between the sponsor and the investigator should state that the investigator agrees to:

- start the trial only after it has been approved by the MHRA and REC
- start and complete the trial within realistic timelines
- undertake all the trial-related duties and functions allocated by the sponsor to the investigator
- carry out the trial according to current regulations, GCP, GMP, all relevant regulatory requirements, and the protocol
- comply with procedures for recording or reporting data
- allow the sponsor's monitors and auditors, as well as the MHRA and REC, direct access to the trial site, source documents, source data, and reports.

Also, the contract should include statements relating to:

- confidentiality, publication policy, payments, reasons for non-payment, stopping of the trial, storing and destroying trial-related documents, any equipment provided by the sponsor, and ownership of trial materials, records and results, and
- the sponsor abiding by Section 19 of these ABPI guidelines about compensation for injury to trial subjects and indemnity for the investigator.

Units that manufacture or import IMPs must have a technical agreement with the sponsor (Section 12).

The sponsor may transfer any or all of their trial-related duties and functions to a contract research organisation (CRO). The CRO must have sound finances, so that they can meet their contractual obligations. However, the sponsor retains overall responsibility for the trial.

# 10 Trial subjects

## 10.1 Recruitment

Potential trial subjects may be recruited:

- from a paper or electronic database of people who have indicated their willingness to take part in a trial
- by advertisements in a newspaper or magazine, on a noticeboard in places such as a university or hospital, on the radio or television, on a website or through social media
- by word of mouth, or
- by referral from another doctor.

All study-specific advertisements must be approved by a REC. The Clinical Trials Directive guidance document on REC applications<sup>23</sup> give advice about advertising for subjects for clinical trials. Advertisements should say that the trial involves research and that the advertisement has been approved by a REC, and should give a contact name and phone number and some of the selection criteria. In addition, advertisements may give the purpose of the trial, where it will take place and the name of the company or institution carrying it out. However, advertisements must never over-stress payment, use REC or MHRA approval as an inducement, name and promote the product, or claim that it is safe.

To ensure consistency, in the UK generic advertising for Phase I studies should seek ethical advice on the procedures. Further guidance can be obtained from Section 5.52 (Review of general advertising and screening procedures at clinical trial units) of version 7.2 of the Standard Operating Procedures For Research Ethics Committees (of the United Kingdom)<sup>31</sup>.

Whatever the method of recruitment, subjects must be recruited of their own free will. They should not be made to feel obliged to take part in a trial, nor should they suffer in any way if they do not take part.

Additionally, they should be recruited only if they:

- are capable of giving valid consent, and
- have been fully and properly informed so that they understand:
  - the nature and purpose of the trial
  - any risks, either known or suspected, and any inconvenience, discomfort or pain that they are likely to experience
  - that they can withdraw at any time and without giving a reason
  - that the investigator may withdraw them at any time if they do not follow the protocol or if their health is at risk.

All units must keep records of subjects who take part in their trials and avoid excessive use of any subject. The number of trials that a subject may take part in during any 12-month period will depend on:

- the types of IMP and their half-lives
- the routes of administration of the IMP
- the frequency and duration of exposure to the IMP
- the procedures involved, and
- the total volume of blood taken from the subject.

Subjects must not:

- take part in more than one trial at a time
- receive more than 10 mSv of radioactivity in any 12-month period if a healthy subject<sup>63</sup>.

In general, subjects should not receive an IMP systemically less than three months after the previous one or five half-lives, whichever is the longest. However, on occasions a shorter interval may be justified, especially when using well-characterised, marketed drugs with a short half-life and little risk of carryover effects.



## 10.2 Monitoring overexposure

Trial subjects must provide proof of identity before they take part in a trial and should be monitored and prevented from taking part in too many trials. The ways to ensure this are:

- counselling the subject
- including warnings in the information leaflet and consent form
- for units to keep a register of their clinical trials and subjects who have taken part in them – keeping photographic evidence of a subject's identity should be considered
- contacting the GP
- being vigilant when screening trial subjects, e.g. looking for evidence, such as needle marks on the forearm and low blood counts, that the subject may have taken part in a trial recently, and
- using an internet-based central register called TOPS<sup>49</sup>, which is run by the Health Research Authority (HRA).

REC applications must include information about procedures for checking simultaneous or recent involvement of potential subjects in other trials.

## 10.3 Special populations

### 10.3.1 Women

The inclusion of women as early as possible in drug development might be a valuable clinical strategy depending on the characteristics of the IMP and on its primary indication.

In the exploratory Phase I trials such as single and multiple ascending doses, women will typically be of non-child-bearing potential being subject to the standard inclusion/exclusion criteria for the trial to be conducted.

However, when a sponsor has decided to include Women Of Child Bearing Potential (WOCBP), particular considerations should be given depending on the speculated magnitude of human teratogenicity/fetotoxicity.

A woman capable of having a child may take part in a trial of an IMP only if:

- the reproductive toxicology studies have been completed and the results raise no concern against participation in

clinical trials<sup>4</sup> or there is a comprehensive rationale as to why reproductive toxicology studies are not needed prior to the inclusion of women (e.g. type of IMP such as biologics, women-only disease type)

and/or

the risk of pregnancy is minimised e.g. because she agrees to adhere to a highly effective method of contraception that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly (highly effective methods to avoid pregnancy are defined in the ICH guideline<sup>4</sup> and as per the Advisory non-binding guidance supported by national competent authorities represented at the CTFG-meeting in Rome 2014-09-1564). Women using a hormonal contraceptive, such as 'the pill', should use an alternative method of contraception until the possibility of an interaction with the IMP has been excluded

- she is not pregnant, according to her menstrual history and a pregnancy test
- she is warned about the potential risks to the developing child should she become pregnant, and
- she is tested for pregnancy before dosing starts and possibly during the trial, as appropriate.

Clinical trials can be purposefully conducted in pregnant women when this is the population sought, e.g. placental transfer studies.

Further documentation is provided in the ICH guideline<sup>4</sup> and in the recommendations related to contraception and pregnancy testing in clinical trials from the Clinical Trial Facilitation Group (CTFG) dated Sept 2014<sup>64</sup>.

### 10.3.2 Children

IMPs should be tested in healthy children only if the circumstances are exceptional and the guidelines for trials in children are followed<sup>65, 66</sup>.

### 10.3.3 Elderly

Trials of IMPs in elderly subjects are justified if the product is intended for use in the elderly, and especially if its effects and metabolism might differ from those in younger subjects<sup>67</sup>.

### 10.3.4 Vulnerable subjects

Investigators must be wary of recruiting vulnerable trial subjects<sup>68</sup>, such as the unemployed, or employees of the company or students of the institution that is sponsoring or carrying out the trial. Employees and students are, or may feel, vulnerable to pressure from someone who can influence their careers. Should such subjects decide to take part in the trial, they must be dealt with like other subjects in the trial, and not be allowed to let their normal work interfere with the trial. The investigator should forewarn employees, in a written agreement, of the possible implications of having their personal data processed at work by their colleagues. Employees and students may need to get permission from their employer or institution beforehand. Some sponsors bar use of employees from trials of IMPs.

### 10.3.5 Patients

All non-therapeutic trials of IMPs – whether they involve healthy subjects or patients – are now called Phase I trials. The following are examples of Phase I trials involving patients.

- Subjects who are well but have a chronic, stable condition – such as asthma, hayfever, type 2 diabetes or hypertension – may be given single doses or short courses of an IMP from which they do not benefit therapeutically. Such trials, especially if they include a challenge agent (Appendix 2), can help decide whether or not to proceed to trials in larger numbers of patients, who may benefit therapeutically.
- The FIH trial of a cytotoxic IMP to treat cancer is often multiple ascending dose in design, to assess the tolerability and PK of the IMP. Such trials have to be carried out in patients.
- Trials on the PK of an IMP in patients with varying degrees of impaired kidney or liver function, and if necessary to recommend adjustments to the dose in such patients. Such trials are difficult to do because of slow patient recruitment and ethical concerns. For those reasons, they are usually carried out late in the development of the IMP.

## 10.4 Obtaining informed consent

Informed consent can be sought by the investigator or a delegate (doctors, healthcare professionals, non-healthcare professionals with appropriate training). They must:

- obtain the consent of subjects only after the REC has approved in writing the information and consent form
- fully inform potential trial subjects before they agree to take part in the trial
- give the subjects oral and written information that is free of jargon and is easy to understand
- give the subjects enough time and opportunity to ask questions about the trial, answer their questions accurately and honestly, and ensure that they understand the answers
- ensure that neither the investigator nor other staff coerce subjects to take part or continue to take part in the trial
- give the subjects, in writing and after approval of the REC, any new information that might make them change their mind about taking part in the trial, and
- ensure that the subjects, and who informs them, sign and date a consent form, and are given a copy.

HRA has issued guidance<sup>69</sup> for writing information and consent forms for clinical trials. The Plain English Campaign<sup>70</sup> gives advice about how to write medical documents for members of the public.

The written informed consent form and any other written information to be provided to subjects for an FIH trial present unique challenges to the author. The document must provide an interpretation of risk derived solely from pre-clinical data and knowledge of the pharmacological target in a way that is easily understood by a lay person. In the choice of site, the sponsor should check that the site has robust consent procedures in place, and should consider the PI's experience in writing or reviewing informed consent documents. Some specifics of the informed consent documentation for FIH clinical trials are different from those of later trials or later phase trials. For example, in most cases with FIH clinical trials, the written informed consent form is drafted by the unit staff rather than the sponsor, and it must contain the rationale in lay language for the start dose and the maximum dose. The critically important information on the drug characteristics (pharmacological and toxicological) to support the start dose and the maximum dose should be provided by the sponsor who also bears a responsibility for the wording being chosen to be easily understood by a lay person. Otherwise, the elements of the informed consent discussion and the written informed consent form must comply with the Good Clinical Practice

standards, which are documented in the Guideline For Good Clinical Practice E6(R2) Note for guidance on Good Clinical Practice CPMP/ICH/135/95 (section 4.8)<sup>19</sup>.

### 10.5 Screening

The investigator should judge trial subjects suitable on the basis of tests, such as:

- a medical history and examination
- medicines taken within a set period before the start of the trial
- a 12-lead ECG
- safety tests of blood and urine
- tests for drugs of abuse - such as alcohol, cannabinoids, cocaine, morphine, benzodiazepines, barbiturates and amphetamines
- tests for HIV, hepatitis B and hepatitis C
- pregnancy tests in women capable of having a child and at risk of becoming pregnant
- trial-specific tests, such as 24-hour ambulatory ECG, echocardiogram, lung function tests, kidney function tests and genetic tests
- for IMPs that affect the immune system: tests to exclude active or recent infections, such as tuberculosis and genito-urinary infection, and willingness not to travel to countries for which vaccinations are intended or that present a higher risk of infectious diseases during the period that the IMP may be active, and
- information from the General Practitioner.

Before subjects decide to have the tests for viruses and for drugs of abuse, the investigator must explain to them what will happen if one of the tests turns out to be positive.

Healthy subjects often have minor out-of-range results of safety tests of blood and urine, and minor variants of the ECG. For example, serum transaminases that are out-of-range<sup>71</sup>, red blood cells in the urine<sup>72</sup>, and nodal rhythm of the ECG<sup>73</sup> are common findings. Some monitors and auditors regard these as deviations from the protocol of a trial in healthy subjects. However, usually they have no clinical relevance and do not justify excluding subjects from a trial. A physician should decide their clinical relevance, and the protocol should allow for use of clinical judgment. If subjects

are deemed unsuitable for a trial, they should be told why.

### 10.6 Timing of recruitment and screening

#### 10.6.1 Panel

Investigators can recruit and screen subjects at any time from a panel of subjects interested in taking part in a Phase I trial, providing the REC has given written approval of the 'screening' protocol and the subjects have given written consent.

#### 10.6.2 Specific trial

Investigators can start to recruit subjects for a specific trial after the REC has given written approval. However, investigators must not screen subjects for a specific trial before obtaining written approval of both the REC and MHRA, and of course the subjects.

If the investigator has approval for panel recruitment and screening, and if the sponsor agrees, the investigator may transfer subjects and their data from a panel to a specific trial, but only after the REC and MHRA have both given written approval for the specific trial and the subject has given written consent for the specific trial. Before transferring subjects, investigators must not carry out procedures that are not covered by the protocol for panel recruitment and screening.

### 10.7 Identification

Subjects who are judged suitable at screening (identity-checked) should be photographed to check their identity at subsequent visits to the unit. Subjects who are resident in the Phase I unit should be fitted with some form of identification, such as a wristband, with the subject's number and trial code. The subject's identity must be checked before carrying out procedures, such as taking blood samples, giving the trial IMP, or recording information in the case report form. The subject's number or barcode should be used on all samples and results.

## 10.8 Informing the subject's General Practitioner

The investigator should ask potential trial subjects for permission to contact their General Practitioner (GP). Subjects who do not have a GP or do not want their GP to be contacted should be excluded from the trial unless there is a good reason to the contrary.

The investigator should inform the GP that their patients have agreed to take part in a trial and should ask if their patients:

- have or have had any relevant illnesses
- are taking or have recently taken any medicines
- have taken part in another clinical trial recently.

The investigator should ask the GP to reply in writing and may offer them payment for responding. The investigator must be able to justify including in the trial a subject whose GP does not give any information. Whether or not the GP responds, the investigator is ultimately responsible for making sure that subjects are suitable for the trial before allowing them to take part in it.

## 10.9 Safety

The investigator must assess the health of trial subjects throughout the trial and should withdraw any subject whose health is at risk. The methods, which should be described in the protocol (Section 8), should include:

- asking subjects about adverse events
- medical examinations
- measuring vital signs such as heart rate and blood pressure
- safety tests of blood and urine
- continuous monitoring of variables such as the ECG and pulse oximetry, and
- trial-specific tests, such as lung function tests.

## 10.10 Follow-up

The protocol should include information on follow-up requirements. For example, the investigator will follow up:

- all subjects after their last dose of IMP, for a period which is indicated in the protocol, depending on the IMP and the trial
- subjects with adverse events, including clinically-relevant abnormal laboratory results, until they have resolved or it is clear that they are resolving, and
- subjects who withdraw or are withdrawn from a trial, as if they had completed it, providing they agree.

# 11 Pharmacy

## 11.1 Premises, facilities and equipment

All units should have a designated pharmacy area that is secure and accessible only to certain staff. The type of premises, facilities and equipment should reflect the types of trial that the investigator does for sponsors. For example, the investigator for a trial of an IMP that is packed and labelled ready for administration to individual subjects will need only basic facilities to store and dispense the IMP, and procedures to keep records of its receipt, storage, use, disposal and retrieval. However, an investigator who assumes some or all of the sponsor's responsibilities for an IMP will need to have the right premises, facilities, equipment and procedures, such as:

- premises that are purpose-built or adapted for the purpose
- the right environment for the dosage form to be manufactured, such as directional air-flow that is controlled for particles, microbiological contamination and temperature, and is monitored appropriately
- a designated storage area, with a quarantine area, for the IMP
- the right equipment, such as a laminar flow cabinet to prepare sterile products
- procedures to comply with GMP<sup>28</sup> and the annexes, especially the current versions of annex 1<sup>25</sup>, annex 13<sup>26</sup>, and annex 16<sup>27</sup>.
- a rigorous quality management system, and
- a Manufacturer's Authorisation [MIA (IMP)]<sup>3</sup> to manufacture, assemble or import IMPs, including placebo and other comparators.

In particular, when designing an FIH trial, the sponsor development team must consider the formulation that will be used and the need for flexibility to permit adjustment of doses in real time as safety and PK data become available (unless an open-label study is planned, matching placebo will also be required for blinding purposes) and whether the pharmacy can appropriately handle those constraints.

For instance, the formulations used in FIH trials have generally not yet been optimised, and the sponsor should therefore identify as soon as possible whether the dosage form will require specific preparation at the research site (for example, dilution for preparation of an intravenous infusion, or preparation of a suspension). The sponsor should pay great attention to the type of licence held by the research site's pharmacy to ensure the study is placed at a site that can perform the preparation. The research site should have an equipped investigational drug pharmacy, staffed with qualified pharmacist/s and/or technician/s who have experience preparing special dosage forms typically used in FIH evaluations (e.g. oral powder for constitution, intravenous formulations requiring dilution steps, etc). The sponsor should ensure that the site pharmacy holds the appropriate manufacturing and assembly licence, such as the MIA (IMP) licence awarded by the MHRA, and that this licence is referenced in the IMP dossier submission to the MHRA, for all sites based in the UK. The sponsor should check that the specific manufacturing or assembly activities that are required for the study are authorised on the licence (e.g. importation of IMPs, sterile products, biological medicinal products, packaging and labelling, storage, blinding). In addition, the sponsor should check that the site pharmacy has timely access to a Qualified Person (QP) who can facilitate issues around release of final product for human administration<sup>74</sup>. If possible, 24-hour 'in-use' stability of the constituted dosage form should be provided, as this will ease the burden on the site in terms of the timing of the preparation vs. the timing of dose administration.

## 11.2 Storage

IMPs should be stored in designated areas under conditions and for times recommended by the sponsor and defined in the IMP dossier, supported by appropriate stability data and defined on the IMP label as applicable. Storage areas should:

- have adequate space for different IMPs to be stored apart
- be temperature-controlled and, if appropriate, humidity-monitored, with alarm controls

- be protected from direct sunlight
- be mapped to identify and avoid using hot and cold spots, if appropriate
- be secure
- be accessible only to authorised staff
- have records for logging IMPs in and out.

The pharmacy should keep a stock of marketed medicines for managing common adverse events – such as headache and nausea – and for managing medical emergencies other than cardiopulmonary resuscitation (Section 17) – such as convulsions and low blood sugar. The sponsor should indicate whether an antidote to the IMP exists and ensure its supply. These medicines must be readily available to clinical staff.

If any rescue medication (non-investigational medicinal products, or NIMPs) are imported from a third country then these must be imported as an unlicensed medicine by the holder of a 'Specials' licence in the UK in accordance with MHRA Guidance Note 14.

### 11.3 Staff

The pharmacy staff must be suitably qualified and experienced, and sufficient in number for the type and amount of work that the pharmacy undertakes.

A registered pharmacist, ideally with manufacturing experience, should prepare or assemble the IMP. A pharmacist may delegate work to pharmacy technicians or assistants, but must supervise their work.

A physician or a pharmacist should have overall responsibility for IMPs and marketed medicines, including emergency medicines.

Holders of an MIA (IMP) must:

- allow the MHRA to inspect the premises at any reasonable time
- have access to a qualified person who is named on the MIA (IMP)
- maintain an effective Pharmaceutical Quality system with adequate facilities, equipment and staff.

### 11.4 Types of work

The work that the pharmacy might undertake, and for which GCP and GMP sets the standards, includes: importing; packaging and labelling; randomisation; manufacture; batch release; sampling and testing; blinding and emergency unblinding; retrieval; and disposal.



# 12 Qualified Person

## 12.1 Requirements

Units with a pharmacy that manufactures, assembles or imports IMPs, including placebo and other comparators, must have an MIA (IMP) on which a qualified person (QP) must be named. A QP is someone who meets the permanent provisions of Directive 2001/83/EC<sup>75</sup> or is someone who met the eligibility criteria during the transitional period after implementation of the Clinical Trials Directive. People who achieved QP status during the transitional period should make sure that their job description accurately reflects the duties of a QP<sup>74</sup> and that they keep up to date with GMP.

## 12.2 Responsibilities

The QP must make sure that:

- each batch of IMP that is made within the EU meets the requirements of GMP and the CTA
- for an IMP made in a third country, each batch meets the requirements at least equivalent to those in the EU, and the CTA requirements
- for a comparator from a third country, if documents are not available to show that it was made in accordance with EU GMP, that it has had all the analyses, tests or checks necessary to confirm its quality in accordance with the CTA.

The scope of the work of the QP will depend on what the sponsor delegates to the unit. For example, a unit might receive, store and account only for an IMP made in the EU, and a QP at the unit need not be involved if the finished IMP has been previously certified by another EU QP. On the other hand, a unit might import the IMP from a third country, obtain evidence that it was made according to GMP, store it, manufacture or assemble batches of it, release it, and account for it, and the services of a QP would be essential.

In an industrial setting, a single QP cannot usually be closely involved with every stage of manufacture, so the QP who certifies a finished product batch may have to rely on the advice and decisions of others. Before doing so, the QP must ensure that the advice is well founded. If another QP confirms compliance with GMP, he or she must do so in writing and state exactly what is being confirmed. The arrangements should be set out in the technical agreement.

## 12.3 Releasing IMP prepared by the pharmacy

It is the role of the QP to release batches of IMP. The manufacture and release of IMP for Phase I trials differs from that of marketed products. Marketed products are usually made in large batches during continuous sessions of work, and a QP releases each batch before it is marketed. Although a Phase I unit may prepare an IMP in one continuous session, it is more usual to prepare an IMP for small groups of subjects or just one subject at a time, and perhaps at unsocial hours. The time between preparing the IMP and giving it to the trial subjects may be a few hours or even minutes. It is not clear what constitutes a batch of an IMP. It is also not practical to have a QP available at all times. Therefore, units should devise a written procedure for releasing IMP and be prepared to justify it during inspection for an MIA (IMP). The QP may have to release some batches retrospectively. However, that should happen only as an exception and stated in the CTA application.

When deciding whether to accept an IMP prepared in the pharmacy for use in a clinical trial, the QP should take the following into account, as appropriate (note this list may not be exhaustive):

- CTA application
- Product Specification File
- the order to request processing and packaging of a batch of IMP
- randomisation code
- protocol and amendments
- pharmacy instructions
- pharmacy SOP
- details of any deviations from procedures and action taken
- production records
- results of QC testing
- certificate of analysis and compliance with current specifications defined in the IMP dossier

- certificate of compliance with GMP from another QP as applicable
- stability data
- inspection of finished product
- environmental monitoring records
- validation, calibration, servicing and maintenance records
- findings of any audits
- IMP accountability and storage records.

## 12.4 Manufacture of IMP

### 12.4.1 European Union or European Economic Area

If an IMP is manufactured in EU countries, an MIA (IMP) is required as part of the CTA application, to show that the IMP has been made to GMP standards. The same applies to an IMP made in the European Economic Area (EEA). The sponsor provides evidence of compliance with GMP, and a QP signs off each batch.

### 12.4.2 Third country: importing an IMP

If an IMP is manufactured in a third country (outside the EU or EEA), the QP named on the MIA (IMP) who authorises importation must certify that the IMP has been made to GMP standards. The QP must submit a declaration - available on [www.mhra.gov.uk](http://www.mhra.gov.uk) - as part of the CTA application.

The EU has negotiated a Mutual Recognition Agreement (MRA) with some countries, and equivalent GMP standards apply to those countries. The latest news of MRA is available on the EMA website<sup>76</sup>. It is important to note that manufacture of IMPs is excluded from the scope of some of these MRAs.



# 13 Investigational medicinal products

## 13.1 Manufacture

Whoever imports, manufactures, assembles or repackages IMPs must apply for and get an MIA (IMP)<sup>3</sup> from the MHRA and must follow GMP. Many of the pharmacy tasks that Phase I units do for sponsors need an MIA (IMP). Some examples are:

- re-packing bulk capsules or tablets into unit-dose containers, and randomising and labelling them
- weighing bulk material directly into capsules
- preparing, under aseptic conditions, a formulation for parenteral use
- importing labelled unit-dose containers from a third country.

During the early stages of development of an IMP, the manufacturing process may change as the sponsor learns more about the product. Therefore, the sponsor's early formulations of an IMP may be primitive and require finishing work by the Phase I unit before they are ready for administration to the trial subjects.

## 13.2 Documents and records

Pharmacies that manufacture or prepare IMPs must have written instructions and records for their manufacturing processes. It should be possible to trace the history of each batch and any changes introduced during IMP development.

The pharmacy should keep records of manufacture, preparation, packaging, quality control, batch release, storage conditions, and shipping of an IMP.

## 13.3 Supplying the investigator

The sponsor should not supply the investigator with an IMP before:

- the CTA application is approved in writing
- the REC application is approved in writing
- the IMP has been certified by the QP and released by the sponsor under the two-step release process
- the code-break is in place
- the technical agreement between sponsor and investigator is in place.

However, the sponsor may release the IMP to the qualified person (Section 12) of the Phase I unit, providing he or she quarantines it until the above conditions have been met.

## 13.4 Transport to the trial site

The sponsor should ensure that the IMP is packed properly and ensure that storage requirements are met during transport to the investigator. Regardless of the IMP transportation conditions (e.g. ambient temperature, cold or frozen) temperature loggers should be added to the container for temperature monitoring.

## 13.5 Accountability at the trial site

The investigator, pharmacist or other delegate should keep records of each stage of the handling and use of an IMP, such as:

- receiving it and assessing its condition on arrival, and notifying the findings to the sponsor
- dispensing or manufacturing it
- giving each subject the dose or doses specified by the protocol
- returning unused product to the sponsor or delegate, or destroying it, as instructed by the sponsor
- keeping an inventory
- reconciling all the IMP received from the sponsor.

These records should include the dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the IMP and to the trial subjects.

The unit must have a system for retrieving/recalling the IMP promptly at any time.

## 13.6 Retention of samples

Manufacturers or importers of the IMP must retain samples of each batch of bulk product, and of the packaging components used for each finished batch, for at least two years after the trial. The reference sample should be of sufficient size to permit carrying out, on at least two occasions, the full analytical controls on the batch in accordance with the IMP dossier. Pharmacies may not be able to meet those requirements if they manufacture only small quantities or individual doses of an IMP, or if the finished product is unstable. In those circumstances, the MHRA may agree to other sampling conditions, which should be described in the protocol or the CTA application.

## 13.7 Randomisation

There should be written procedures as appropriate for generation, distribution, handling and retention of any randomisation code used for packaging an IMP.

## 13.8 Emergency unblinding

The investigator or delegate must have a written procedure for rapidly identifying a 'blinded' IMP in an emergency. The procedure must be secure, readily available at all times during the trial, and not allow breaks of the blinding to go undetected. It is also important that an investigator can unblind a subject's treatment allocation immediately, without having to first contact any trial staff or the sponsor.

## 13.9 Quality management

Manufacturing and dispensing IMPs is more complex than manufacturing and dispensing marketed products, due to:

- production processes that are often not validated
- the lack of fixed routines
- the increased risk of contamination, including cross-contamination
- the need for blinding and randomisation in most trials.

Therefore, units must have robust quality control and quality assurance procedures for manufacturing and dispensing IMPs. The people responsible for manufacturing and dispensing should be independent of those responsible for quality management.

# 14 Biotechnology products

## 14.1 General

Examples of biotechnology IMPs (also called biological IMPs) are: recombinant proteins, hormones, cytokines, monoclonal antibodies, genetically modified micro-organisms (GMM) and gene therapy. They are regulated differently from other IMPs, as follows.

- They need different pre-clinical studies to support clinical trials<sup>21</sup>.
- The Clinical Trials Directive allows the MHRA and REC an extra 30 days to review trials of gene therapy, somatic cell therapy or GMM. It allows another 90 days to consult others.
- Clinical trials of gene therapy need approval of the Gene Therapy Advisory Committee (GTAC)<sup>77</sup> in addition to the MHRA.
- Clinical trials of live GMM must follow the Health and Safety Executive regulations controlling contained use of GMM<sup>78</sup>. Guidance on risk assessment and containment is available from [www.hse.gov.uk](http://www.hse.gov.uk).
- The MHRA handles trials of higher risk biological IMPs differently from trials of other IMPs (Section 13).

## 14.2 Proteins and monoclonal antibodies

Units must have the appropriate experience, facilities, and staff to do trials of these types of IMPs. The investigator must be capable of managing immune reactions, including anaphylactic reactions<sup>79</sup>. Proteins often have long half-lives, and are designed for infrequent dosing regimens in patients. Thus, depending on the molecule's characteristics, there should be enough follow-up of subjects – three months or even longer – to obtain a full PK profile and to allow reliable assessment of the immune response.

## 4.3 Gene therapy

Gene therapy is the deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes. Examples include genetically modified viral vectors and naked DNA injection. GTAC has issued guidelines for applications for gene therapy trials<sup>77</sup>, and expects the investigator to have:

- a substantial multidisciplinary team of researchers
- suitable clinical and laboratory facilities
- on-site support, such as infection-control measures
- a proven track-record of high-grade clinical research.

Investigators who are unsure if an IMP is gene therapy, or if it is appropriate to give it to healthy subjects, should seek advice from GTAC. GTAC has approved certain non-therapeutic trials of gene therapy in healthy subjects.

## 14.4 Genetically modified micro-organisms (GMM)

Some GMM, such as vaccines containing genetically-modified viruses intended to raise a prophylactic immune response to the wild virus, can be given to healthy subjects. GTAC does not normally wish to review such trials.

# 15 Radioactive substances

## 15.1 General

Radioactive substances contain a radioactive isotope. Examples of radioactive substances that may be given to healthy subjects are:

- radiolabelled IMPs - usually with  $^{14}\text{C}$  but also  $^3\text{H}$ ,  $^{99\text{m}}\text{Tc}$  and other isotopes - to assess their absorption, metabolism, elimination and gastrointestinal transit as well as the performance of individual product formulations
- imaging agents - such as receptor ligands labelled with  $^{11}\text{C}$  or  $^{18}\text{F}$  for PET (positron emission tomography) scans, and ligands labelled with  $^{99\text{m}}\text{Tc}$  for SPECT (single photon emission computed tomography) scans - to produce images of organs such as the brain or heart
- biological products - such as red blood cells labelled with  $^{51}\text{Cr}$  or proteins labelled with  $^{131}\text{I}$  - to assess their lifespan
- radiolabelled products with which to assess the effect of an IMP on normal function, such as  $^{51}\text{Cr}$ -EDTA to assess renal function, and  $^{99\text{m}}\text{Tc}$  to assess cardiac function.

Administration of radioactive substances is governed by the Medicines (Administration of Radioactive Substances) Regulations (MARS)<sup>80</sup> and the Ionising Radiation (Medical Exposure) Regulations (IRMER)<sup>81</sup>.

Clinical trials of radioactive substances must follow the Ionising Radiations Regulations<sup>82</sup> and must be approved by the Administration of Radioactive Substances Advisory Committee (ARSAC) before they can start. ARSAC decides if the radiation exposure that the trial subjects are to receive is within acceptable limits. ARSAC guidelines<sup>83</sup> state that the radiation dose should be as low as reasonably practical in healthy subjects, and should not exceed 10mSv annually.

A hospital department of nuclear medicine may have a licence to use a radionuclide, such as  $^{99\text{m}}\text{Tc}$ , for routine diagnostic purposes in patients. However, a clinical trial involving  $^{99\text{m}}\text{Tc}$  in healthy subjects still needs ARSAC approval.

It is important to note that radiolabelling of an IMP is a different activity from 'labelling' in the sense of applying labels with the required information on the finished IMP pack as described in Annex 13.

## 15.2 Microdose/microtracer trials

As mentioned in Section 1, a microdose study is a non-therapeutic study with a very low dose of IMP. A microdose is defined as less than one hundredth of the predicted pharmacological dose but not exceeding 100 micrograms as single dose<sup>9, 83</sup>. Because the risk of harm from a microdose is much lower than a pharmacological dose, fewer or different pre-clinical studies are required to support a microdose trial. These studies can be conducted without a radiolabel if an assay with a sufficiently low limit of detection is available. More frequently these studies are conducted with a low dose of radiolabelled IMP with analysis done via AMS (accelerator mass spectrometry)<sup>84</sup> or other very sensitive analytical techniques.

A microtracer study uses microdose levels of radiolabelled drug substance (e.g.  $^{11}\text{C}$ ,  $^{14}\text{C}$ ) to investigate human pharmacokinetics (PK) as part of the early drug development programme, normally administered on top of an unlabelled oral therapeutic dose. For example, a radiolabelled IV microtracer dose can be administered to coincide with the  $C_{\text{max}}$  of a non-labelled oral dose to calculate absolute bioavailability. A very low dose (less than 1  $\mu\text{Sv}$ ) of radiation does not need ARSAC approval<sup>63</sup>.

## 15.3 Premises, facilities and equipment

The premises must be located, constructed and maintained to suit the operations to be carried out in them, and must be registered by the Environmental Agency under the Radioactive Substances Act 1993<sup>85</sup> to keep, use and dispose of radioactive materials. Sites that manufacture radiopharmaceutical products must comply with specific GMP guidelines<sup>86</sup> as well as standard GMP guidelines. When making an ARSAC application for a trial, investigators must provide evidence of the suitability of:

- the equipment to undertake the procedure involved
- the working areas and related equipment
- the staff to supervise, dose and nurse the trial subjects.

For example, a trial of a radiolabelled IMP to assess its absorption and metabolism needs only facilities to collect specimens of the subjects' blood, urine and faeces, a suitable counter to measure radiation, for safety purposes, and access to a laboratory scintillation counter to measure radioactivity in the specimens. In contrast, a trial involving an imaging agent, such as a ligand labelled with  $^{11}\text{C}$  or  $^{18}\text{F}$  for PET scans, needs much more sophisticated resources, including access to a cyclotron unit to make the ligand, and a PET scanner to measure binding to the receptor site.

### 15.4 Staff

The investigator must hold a certificate from ARSAC to administer or supervise the administration of radioactive substances. Applicants for certificates are normally of consultant status and supply information on their training and experience as well as on the services – such as departments of radiopharmacy and medical physics – that support them. Other staff should be suitably qualified and experienced. There must be a Radiation Protection Supervisor whose work must be supervised by the area Radiation Protection Adviser. Trials of radioactive substances usually need the collaboration of several groups of experienced researchers.

### 15.5 Trial subjects

When selecting healthy subjects for trials of radioactive substances<sup>63</sup>, the investigator should:

- study subjects over 50 years old whenever possible, unless younger subjects can be justified
- study as few subjects as possible
- exclude women capable of having a child
- not expose subjects to more radiation than necessary
- exclude subjects exposed to radiation during their work
- exclude classified radiation workers
- exclude subjects who have received more than 10 mSv of radioactivity in the past 12 months.

## 16 Non-investigational medicinal products

Non-investigational medicinal products (NIMPs) are often used during Phase I trials:

- to induce a physiological or pharmacological response to assess the activities of an IMP (in which case they are often called challenge agents), or
- as support or escape medication for preventative, diagnostic or therapeutic reasons.

Under these circumstances, they do not fall within the definition of an IMP<sup>26</sup>, and investigators who prepare them do not need an MIA (IMP). Nor does a trial of a non-IMP by itself require a CTA.

An algorithm defining what does and does not constitute a NIMP can be found on the MHRA's website<sup>39</sup>. The site also contains a file with mock examples of NIMPs.

Further guidance on the requirements for and the use of NIMPs can be found in the European Union's Guidance on Investigational Medicinal Products (IMPs) and Other Medicinal Products used in Clinical Trials, Volume 10, Chapter 5<sup>23</sup>.

If it is necessary for the NIMP to be imported from a non-EEA country due to there being no EU-licensed product available, then this may require importation as an unlicensed medicine and should be undertaken by the holder of a Manufacturers Specials licence (MS) in the UK following the principles of MHRA Guidance Note 14.

## 17 Resuscitation procedures, equipment, medicines and training

There must be procedures, equipment, medicines and trained staff to deal with any medical emergency that might arise during a trial, as follows.

### 17.1 General procedures

Trial subjects must:

- have a call button by their bed and in places such as social areas, toilets and showers, to call trial staff
- be given the names and telephone numbers of the trial physicians, so that the subject (or another doctor who might see the subject) can call the 'on-call' physician or a trial physician at any time.

Trial staff must have access to, and must be trained in the following:

- medical cover throughout the trial
- an 'on-call' doctor who they can contact by telephone at any time

- the sponsor's medical monitor or defined delegates whom they can contact by telephone at any time. A cascade of contactable personnel on the sponsor's side should be available to the investigator site – this can be added to the study protocol or be detailed in a separate document
- a procedure to report serious adverse events
- a procedure to break the blind, should a subject have a severe adverse event
- an alarm system, to call for assistance in case of a medical emergency
- continuous monitoring of vital signs, such as ECG and pulse oximetry
- procedures for dealing with the most likely medical

emergencies<sup>79</sup>, such as profound syncope, hypotension, anaphylaxis and cardiopulmonary arrest

- a procedure to transfer a trial subject to hospital (see below).

## 17.2 Resuscitation equipment and medicines/antidote

In each of the main clinical areas of the premises, there must be a resuscitation trolley with equipment and medicines that can be moved quickly to where they are needed in a medical emergency. Each trolley should have the same equipment and medicines, which must be checked at least weekly and after use, and records of the checks must be kept. The main items on each trolley should be as those recommended by the Resuscitation Council<sup>79</sup>, for example:

- a defibrillator with an ECG monitor (both mains and battery operated)
- suction apparatus
- an oxygen cylinder and flowmeter
- oropharyngeal airways and face masks
- a self-inflating bag
- a laryngoscope and endotracheal tubes or laryngeal mask/alternative supraglottic airway device
- consumables such as intravenous cannulae and fluid infusion sets
- emergency medicines, including intravenous fluids
- a transcutaneous cardiac pacer (one should be enough for the whole premises)
- waveform capnograph with appropriate tubing and connector.

If there is an antidote to the IMP being tested, it must be readily available at all times. The same applies to NIMPs.

## 17.3 Resuscitation training

Physicians, nurses and other staff who help to care for trial subjects must all be trained and hold a valid certificate in basic (BLS), immediate (ILS), or advanced life support (ALS) procedures, as appropriate<sup>79</sup>. For example, all physicians must be trained and hold a valid certificate in ALS or ILS.

The medical director or another doctor with clinical expertise in resuscitation should set and maintain standards of training and assessment of the unit's staff, and ensure that competence is maintained by regular refresher training. Appropriately trained people, such as doctors and resuscitation training officers, should carry out the training and assessment.

Further guidance on training requirements for clinical staff and medical cover can be found in Appendix 1 of the MHRA's Phase I Accreditation Scheme requirements document<sup>47</sup>.



# 18 Confidentiality

## 18.1 Sponsors

Sponsors expect investigators to keep confidential any commercially-sensitive information, such as the protocol, investigator's brochure, IMP dossier, and case report form (CRF). Trial subjects who ask to see the protocol should be allowed to do so, but not be allowed to keep a copy.

A statement about confidentiality is normally included in the trial protocol or contract. Therefore when trial-related documents are not in use, trial staff must store them in a secure place with access limited to authorised people - the trial staff, the sponsor's monitors and auditors, the REC, and the MHRA and other regulatory authorities. An investigator who undertakes trials for different sponsors should keep the trials apart while they are in progress on the unit. In addition, the monitors and auditors of different sponsors should have separate spaces in which to work during site visits.

## 18.2 Trial subjects

The investigator should give each trial subject a unique identifier to conceal the subject's identity when recording and reporting trial-related data. However, the investigator must identify the subject when contacting the subject's GP.

If employees or students of the company or institution that is sponsoring or carrying out the trial wish to take part in it, the investigator should forewarn them of the possible implications of having their personal data processed at work by their colleagues.

## 18.3 Data Protection Act

The Data Protection Act<sup>87</sup> covers the processing of personal data, whether written or electronic, of trial subjects. The investigator should comply by:

- entering on a national register details of all the classifications of data held, the subjects and the recipients
- obtaining the subjects' consent for their personal data to be processed
- using personal data only for the purposes set out in the protocol and the information and consent form

- making sure that personal data are relevant to the trial, accurate, not excessive and kept for no longer than necessary
- keeping paper and electronic documents in lockable offices, archives or storage cabinets, and allowing access only to authorised people
- making sure that personal data stored on computers are secure so that only authorised people can change or delete them
- telling subjects in the information and consent form that they may see information about themselves on request
- not transferring personal data outside the EU without adequate protection.

## 18.4 Human Tissue Act

Investigators must have informed consent from the trial subjects and approval from the REC to take any samples of tissue. Consent may be sought for long-term storage and future research as well as for use in the specific trial. Under the Human Tissue Act<sup>88</sup>, REC approval makes it lawful to store and use the samples for the specific trial only. Licensed establishments that continue to store samples after the trial has ended – either for their own research or to distribute to other researchers – are acting as a tissue bank, and must obtain a storage licence from the Human Tissue Authority<sup>88</sup>.



# 19 Compensation, indemnity and insurance

## 19.1 Compensation

For many years the ABPI has required that special provisions should apply to the provision of compensation to subjects involved in healthy subject studies and patient studies that are sponsored by industry. However, different compensation provisions were applied to healthy subject studies and to patient studies. In 2014 a cross-sector group convened by the ABPI released new guidance on compensation which reflected that an increasing number of studies at Phase I now involve patients as well as (or instead of) healthy subjects<sup>89</sup>. The patients with the target disease participating in these studies at Phase I are not expected to gain therapeutic benefit and would not ordinarily be offered access to the medicinal product under investigation beyond the end of the study. In these circumstances, it is no longer thought ethically appropriate to distinguish between the compensation arrangements benefiting healthy subjects and patient subjects.

Oncology or other studies at Phase I where more side effects are foreseeable because of the nature of the product under research, but where patient subjects may reasonably expect to receive therapeutic benefit, are not affected by this change of policy.

The nature of the compensation policy should be clear from the information and consent form, and subjects should be invited to seek explanation of any aspect of the undertaking that is not clear to them. It must be clear that appropriate compensation will be paid without the subject having to prove either that such injury arose through negligence or that the product was defective in the sense that it did not fulfil a reasonable expectation of safety.

Subjects may make a claim directly to the sponsor or through the investigator. The sponsor should involve the investigator in any discussions with trial subjects about their right to compensation.

## 19.2 Payments

The HRA National Research Ethics Advisors Panel has endorsed guidance produced by the Phase I Advisory Group on Incentives in Phase I trials, which is very useful<sup>90</sup>. Many trials are demanding of the subject and involve long periods of residence, many visits to the trial site, urine collections, and multiple blood tests and other procedures that cause discomfort, as well as lifestyle restrictions. So it is right to pay subjects – healthy subjects and patients – who volunteer for non-therapeutic Phase I trials more than just any expenses that they incur. The amount should be related to the duration of residence on the unit, the number and length of visits, lifestyle restrictions, and the type and extent of the inconvenience and discomfort involved but not on perceived risks. As a guide, payments should be based on the minimum hourly wage and should be increased for procedures requiring extra care on the part of the subject or involving more discomfort.

Subjects who withdraw or are withdrawn even for medical reasons should not always be paid the full amount. The investigator should decide the amount of payment depending on the circumstances. Payment may be reduced, if a subject does not follow the protocol, or may be increased, if the protocol is amended to allow further tests or visits.

If a trial is postponed or cancelled, subjects may be paid for setting aside time to do the trial. Reserve subjects, who 'stand by' in case someone drops out or is withdrawn from the trial before first dosing, should be paid.

The policy on paying trial subjects, and the amount, must be stated in the subject information leaflet and be approved by the REC.

### 19.3 Indemnity

Before the start of a commercially sponsored Phase I trial, the sponsor must indemnify the investigator against any loss incurred by the investigator (including the cost of legal representation) as a result of claims arising from the trial, except to the extent that such claims arise from the negligence of the investigator for which the investigator remains responsible.

### 19.4 Insurance

In relation to the sponsor's obligation to comply with the above compensation policy, the sponsor must ensure that insurance or indemnity is in place to cover its liability and that of the investigator.

The Phase I unit must have insurance to cover claims for negligence, or must provide evidence of financial resources to meet any such claim. Also, physicians involved with the trial must have insurance – such as that offered by a medical defence organisation – that will respond to any negligence claim. Nurses must hold professional indemnity insurance: for example, that which is provided by membership of the Royal College of Nursing.

The sponsor and investigator must be able to satisfy the REC and MHRA that subjects who take part in a Phase I trial are adequately protected against injury. In addition, the sponsor and investigator should do everything possible to ensure that a subject who is involved in a compensation claim is dealt with sympathetically and quickly.

Detailed guidance on insurance and compensation in the event of injury in Phase I clinical trials was developed by a cross-sector group convened by the ABPI<sup>89</sup>.

## 20 Pharmacovigilance

Although the sponsor has overall responsibility for monitoring the safety of its IMP, the investigator and sponsor should work together to help the sponsor meet their obligations.

The investigator must:

- record all adverse events (AE), including abnormal laboratory results, as instructed in the protocol
- report to the sponsor, within the time-frame identified in the protocol, all serious adverse events (SAE), except those identified as exempt in the protocol or investigator's brochure
- provide follow-up reports of SAEs, and any other information requested, within the time-frame identified in the protocol.

The sponsor must:

- report to the MHRA:
  - suspected unexpected serious adverse reactions (SUSARs) that occur in the trial and are associated with any IMP used in the trial
  - SUSARs that are associated with any IMP used in the trial and that the sponsor learns about from other sources, for example, a SUSAR that occurs in another trial
- report to the REC:
  - SUSARs that occur in the trial at a site in the UK and are associated with any IMP used in the trial<sup>31</sup>
  - SUSARs that are associated with use of any of the IMP in the UK (for example a SUSAR in another trial), if the IMP is not marketed in the EU
- report to the investigator(s):
  - SUSARs, as they occur, without unblinding the investigator.

Where a trial is conducted in more than one site/country or different trial with the same IMP is undertaken elsewhere, the sponsor's reporting duties extend to all other involved investigators, ethics committees, and health authorities.

Sponsors must report fatal or life-threatening SUSARs to the MHRA and REC within 7 days, and provide further information within another 8 days, and report all other SUSARs within 15 days.

Sponsors may delegate their responsibilities to the investigator, providing the investigator is not unblinded in the process.

# 21 Pathology laboratory

## 21.1 General

All units should have access to a pathology laboratory for assays of blood, urine and other body fluids. Some units may have their own laboratory, whereas others may use a subcontractor.

The laboratory should have external accreditation, such as Good Laboratory Practice (GLP)<sup>91</sup>, College of American Pathologists (CAP)<sup>92</sup>, Clinical Pathology Accreditation (CPA)<sup>93</sup> or ISO 17025. It should be inspected regularly and participate in continual improvement schemes, such as NEQAS<sup>94</sup>.

## 21.2 Premises, facilities, equipment and procedures

The pathology laboratory should:

- be purpose-built or adapted for the purpose
- have automated equipment for routine haematology, biochemistry and serology tests
- have procedures for analyser calibration and quality control
- regularly maintain all the equipment, including point-of-care equipment
- have a procedure for transporting samples safely and quickly from clinical areas to the laboratory
- have written procedures for all assays, and validate the assays
- have a stock control procedure to make sure that reagents and consumables are used within their expiry dates
- keep records, including source documents and final reports
- have a procedure for authorising and releasing results
- have a procedure for 'flagging' and notifying medical staff of abnormal results
- have a laboratory information management system, and validate and back up the system
- provide protective clothing and safety equipment for staff
- have a central alarm system for all fridges and freezers
- have an internal audit programme.

## 21.3 Staff

The number and type of laboratory staff will depend on the workload, the complexity of the work, and the extent to which the equipment is automated and computerised.

Laboratories usually have a head of department, with a professional qualification such as FIBMS, who is responsible for the scientific and technical work, staff management and training, and administration.

There should be enough trained and competent staff to ensure a good service for specimen turnaround times, completion of acute work on the day of its receipt, and arrangements for urgent specimens. All staff must follow the laboratory's SOP and the Institute of Biomedical Science guidelines<sup>95</sup>, and receive GCP training.

## 22 Data management, statistics, report and publication

### 22.1 General

Sponsors may do their own data management and statistics on trial data or may subcontract it to a unit with the appropriate facilities and staff. Whoever does it, the credibility of the numerical results of the trial depends on the quality and validity of the methods and software used.

### 22.2 Data management

Data management includes data entry, storage, verification, correction and retrieval. Data managers should:

- have computer systems that:
  - are validated, secure and allow only authorised access to the data, and
  - contain an internal audit trail, so that all changes to the data are documented and that entered data are not deleted
- back up each trial database
- test the database set-up and verification checks for each trial with dummy data before any trial data are entered
- enter the data twice, or once with 100% check of data
- keep records of all queries and their resolution
- have a formal procedure for locking and unlocking the database.

Data released to Data Monitoring Committees / Data Safety Monitoring Boards for the purpose of making dose escalation decisions should undergo quality control and be kept in the Trial Master File.

### 22.3 Statistics

There should be a statistical analysis plan (SAP) for each trial<sup>96</sup>. The analysis plan could either be a stand-alone document or be integrated into the protocol. A statistician should:

- write and sign off on the analysis plans before the trial data are available and before any analysis has started
- describe in the protocol or SAP the hypotheses being tested and how conclusions will be drawn, the analyses that will be done, the procedures for dealing with missing data and avoiding bias, and the selection of subjects to be included in the analyses
- put sample tables and listings in the SAP, to show how data will be presented
- include any planned interim analyses in the SAP
- describe and justify in the trial report any deviations from the SAP
- ensure all steps of the data management, reporting and analysis process have fully validated procedures to avoid the potential for errors. These procedures would normally be included in a company's Standard Operating Procedures library.

The Report of the Royal Statistical Society<sup>97</sup> gives guidance about the statistical aspects of FIH trials.

## 22.4 Report and publication policy

Whether the trial is completed or stopped prematurely, the sponsor should ensure that an end-of-trial report is prepared from the data and is given to the investigator, for comments and signature. The report should be based on the ICH Guideline for Clinical Study Reports<sup>98</sup> and has to be submitted to the MHRA within one year of the end of the trial.

The trial findings should be published as an electronic and/or paper document, within a reasonable time after the end of the trial. The sponsor and investigator should agree the publication policy in the protocol or contract, before the start of the trial. The sponsor must be allowed enough time to obtain any patent protection. Either party may prepare a manuscript for publication in a peer-reviewed journal. Each party should allow the other at least 30 days to comment before any results are submitted for publication. Authorship should reflect work done by both parties, in accordance with recognised principles of scientific collaboration.

## 22.5 Staff

The statistician, data managers and data entry staff should be suitably qualified and experienced. Data managers should be life science graduates or of similar status. PK data should be interpreted by an expert in PK.

## 23 Essential documents, trial master file and archiving

### 23.1 Trial master file

The investigator must keep a trial master file<sup>23</sup> of essential documents that:

- allow regulatory agency inspectors to assess how the trial was done, and the quality of the data
- show whether the trial followed the relevant EU Directives, including the Clinical Trials Directive, GCP Directive and GMP Directive.

Essential documents should be:

- generated and on file before the trial starts
- added to the files during the trial, to show that any new information is documented as it becomes available
- in the file after the end of the trial.

### 23.2 Quality of documents

Essential and supporting documents:

- should be complete, legible, genuine, traceable to a specific trial, and readily available to the sponsor and MHRA upon request
- should not be altered without permission and creation of an audit trail, particularly if the documents are stored on electronic, magnetic, optical or similar media
- may be copied or transferred to other media for archiving, if the method has been validated to ensure that information will not be lost or altered and if the copies or transfers are certified for accuracy and completeness
- should be readily available in printed form, if stored on media that require processing.

### 23.3 Storage of documents

A specific person, an archivist, should store trial documents. The archivist should:

- have enough dedicated space that is suitable to store documents from all current trials on site and to store documents from all completed trials either on-site or off-site in a commercial archive
- have storage facilities that are secure and adequately protected from fire, flood, pests, extremes of temperature and humidity, and unauthorised access
- inform the sponsor about the arrangements for storing documents, and about any changes to the arrangements
- notify the sponsor if the investigator becomes unable to store trial documents, so that the sponsor can arrange for them to be stored elsewhere.

### 23.4 Duration of storage

Essential and supporting documents, including the trial subjects' records, must be archived until at least five years after the end of the trial. Access to documents must be restricted to the people with responsibility for archiving:

- until at least two years after the last approval of a marketing application in the EU and until there are no pending or intended marketing applications in the EU, or
- until at least two years after stopping the development of the IMP, or
- for a longer period, if required by the MHRA or the sponsor.

### 23.5 Disposal of documents

The investigator must not destroy any essential documents without the sponsor's permission. The reasons should be recorded and the records kept for at least five years. Sponsors should inform the Phase I unit when the retention period is over.



## 24 Project management and monitoring

Some sponsors allocate a project manager to every Phase I trial, to manage the administrative aspects of the trial, and a monitor, to carry out the traditional duties of a monitor. Other sponsors may have one person to do both jobs. The project manager and monitor should be life science graduates or of similar status. They should be trained in GCP, the relevant aspects of GMP and monitoring, as appropriate.

Nowadays, commercial CROs conduct most Phase I trials. The project manager and/or monitor should:

- know the pre-clinical data and be able to deal with any concerns that the investigators might have about the risk assessment, by arranging for them to discuss their concerns with the sponsor's physician or pre-clinical staff
- assist the investigator in obtaining from the sponsor in good time any documents required to support applications to the REC or MHRA
- ensure that all the trial documents and the IMP are delivered in good time for the trial to start on schedule
- monitor the trial for GMP compliance – if the unit manufactures, assembles or imports the IMP – as well as for GCP compliance
- schedule monitoring visits for key days of the trial, such as when the IMP is first administered, the dose is increased and a non-IMP is administered
- get the sponsor to provide the investigator in good time with any PK data that are needed before the dose can be increased in a dose-rising trial, and
- participate in and document, if appropriate, any discussions between the sponsor and the investigator before the dose is increased, and ensure that the protocol is followed.

# 25 Quality management

## 25.1 Quality system and quality control

The sponsor is ultimately responsible for the quality and the integrity of the trial data. However, all units should have their own system, such as ISO 9001, for quality control and quality assurance, which the staff must follow. The scope of the system and the number and types of staff who operate it will depend on the size of the unit and the sort of work carried out.

All units should have written, authorised procedures and should:

- keep a current version of each procedure at each point of use
- remove obsolete versions from circulation, but keep copies for reference
- review the procedures regularly
- inform relevant staff of any changes to procedures or of any new ones, and train those staff, if necessary, and
- keep records that make it possible to trace which version of a procedure was current at any given time.

Trial staff should check each stage of the trial to ensure that the regulations are being followed and that the data generated are correct.

## 25.2 Auditors

Auditors should:

- be life science graduates or of similar status
- be trained in auditing
- be independent of whatever they audit - if a unit does not have its own independent auditor, the sponsor or a subcontractor may conduct the audit
- regularly audit the quality system
- audit the validation of computerised systems
- regularly audit the facilities, and frequently-used subcontractors such as laboratories, against the relevant sections of these ABPI guidelines

- know the details of the unit's quality system and of Directives such as 2001/20/EC, the guidance documents, GCP, GMP, GAFREC and SOP of RES, MHRA regulations, and other relevant documents
- check whatever tasks have been delegated to the investigator by the sponsor against those documents as well as the protocol, and
- devise and follow an audit plan based on the type and complexity of the trial, the number of subjects and any problems encountered.

## 25.3 Audits

A full clinical trial audit should include:

- the CTA and REC applications
- the trial documents - protocol, information and consent form, blank CRF, and the trial report
- the trial procedures
- the presence, completeness and accuracy of essential documents in the trial master file
- the case report forms and source documents
- the trial database and statistical analysis
- a written report of the audit findings for the investigator and other relevant staff, and
- an audit certificate for the trial master file.
- The sponsor's auditors should audit the unit's facilities or systems or a specific trial, as necessary.

## 26 Health and safety

Units must have a health and safety at work policy<sup>99</sup>, and policies or procedures for the relevant parts of the legislation, including:

- safety in the workplace
- personal protective equipment
- equipment and electrical safety, and
- control of substances hazardous to health (COSHH)<sup>100</sup>.

Units should follow the guidelines of the Advisory Committee for Dangerous Pathogens for containment level 2 as a minimum<sup>101</sup>. All staff at risk of contact with body fluids should be vaccinated against hepatitis B. In addition, there must be a policy to prevent and manage needlestick injuries<sup>102</sup>.

Units that prepare and serve food must follow the Food Safety Regulations. Kitchens and areas where food is served must be kept clean and disinfected. Food must be prepared and stored hygienically, and served at the right temperature<sup>103</sup>.

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## 28 Websites

Acts of Parliament and Statutory Instruments

[www.hmso.gov.uk](http://www.hmso.gov.uk)

Administration of Radioactive Substances Advisory Committee (ARSAC)

<http://www.arsac.org.uk>

Association of the British Pharmaceutical Industry (ABPI)

[www.abpi.org.uk](http://www.abpi.org.uk)

Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI)

[www.ahppi.org.uk](http://www.ahppi.org.uk)

BioIndustry Association (BIA)

<http://www.bioindustry.org/home/>

Clinical and Contract Research Association (CCRA)

<https://www.ccra.org.uk/>

Clinical Pathology Accreditation, UK (CPA)

<http://www.ukas.com/services/accreditation-services/clinical-pathology-accreditation/>

College of American Pathologists (CAP)

<http://www.cap.org/apps/cap.portal>

Data Protection Act

<http://www.legislation.gov.uk/ukpga/1998/29/contents>

Declaration of Helsinki

<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

EudraCT database

<https://eudract.ema.europa.eu/>

European Commission: implementing texts for Directive 2001/20/EC

[http://ec.europa.eu/health/human-use/clinical-trials/index\\_en.htm](http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm)

Gene Therapy Advisory Committee (GTAC)

<http://www.hra.nhs.uk/resources/applying-to-recs/gene-therapy-advisory-committee-gtac/>

Health and Safety Executive

<http://www.hse.gov.uk/>

Health research ethics committees: governance arrangements

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_126474](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_126474)

ICH Guideline for Good Clinical Practice

[http://www.emea.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002874.pdf](http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf)

Medicines and Healthcare products Regulatory Authority (MHRA)

<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>

Medicines for Human Use (Clinical Trials) Regulations

[www.hmso.gov.uk/si/si2004/20041031.htm](http://www.hmso.gov.uk/si/si2004/20041031.htm)

NHS Health Research Authority

<http://www.hra.nhs.uk/>

Resuscitation Council (UK)

<http://www.resus.org.uk>

The Over-Volunteering Prevention System (TOPS)

<https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/>

# Appendix 1: Qualifications relevant to Phase I trials

## Diploma in Pharmaceutical Medicine

The primary qualification for pharmaceutical physicians is the Dip Pharm Med, awarded by the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians (FPM). It can be obtained by sitting an examination (<http://www.fpm.org.uk/trainingexams/exams/dipharmmed>).

There are courses available geared to supporting candidates for the examination.

## Diploma in Human Pharmacology

Developed by the FPM, the Diploma and Certificate in Human Pharmacology (DHP and CHP) have been structured specifically to fit the needs of all with an interest in exploratory drug development.

### Diploma Programme

The DHP is a 2-year programme of structured training for doctors to attain and demonstrate competence to serve as a PI for exploratory studies of IMPs in man. It is anticipated that the DHP will become the primary qualification for PIs.

### Certificate Programme

The CHP is a 1-year part-time programme for doctors and scientists to attain and demonstrate a comprehensive knowledge of all aspects (design, monitoring, analysis, reporting, safety, ethics, regulation and law) of exploratory studies of IMPs in man.

These integrated training programmes address the requirements of PIs and all scientists involved in Phase I studies, whether based in CROs, pharmaceutical companies, universities or regulatory authorities. Information on the DHP and CHP programmes and exams can be found at: [www.fpm.org.uk](http://www.fpm.org.uk). Details and dates of the accredited compulsory Diploma and Certificate courses provided by King's College London can be found at: <http://www.pharm-med.kcl.ac.uk/fpm.html>.

## MSc

The modular MSc in Clinical Pharmacology run by the University of Surrey is tailored to physicians, nurses and life science graduates working in the pharmaceutical industry. Barts, the London School of Medicine and Dentistry, part of the Queen Mary University of London, runs an MSc course in early drug development ([www.mds.qmul.ac.uk](http://www.mds.qmul.ac.uk)).

The Universities of Aberdeen ([www.abdn.ac.uk](http://www.abdn.ac.uk)) and Glasgow ([www.gla.ac.uk](http://www.gla.ac.uk)) run MSc courses in Clinical Pharmacology.

The European Centre of Pharmaceutical Medicine in Basel awards a Diploma in Pharmaceutical Medicine ([www.ecpm.ch](http://www.ecpm.ch)), as does the Claude Bernard University of Lyon ([www.univ-lyon1.fr](http://www.univ-lyon1.fr)).

The Universities of Glamorgan ([www.glam.ac.uk/courses](http://www.glam.ac.uk/courses)) and Liverpool John Moores ([www.livjm.ac.uk](http://www.livjm.ac.uk)) run MSc courses in subjects allied to clinical pharmacology.

## Pharmaceutical Medicine Specialty Training

Clinical pharmacology is a core component of the modular training courses for Pharmaceutical Medicine Specialty Training that lead to accreditation in Pharmaceutical Medicine by the FPM ([www.fpm.org.uk](http://www.fpm.org.uk)).

Physicians employed in academic and hospital clinical pharmacology units can train for accreditation in clinical pharmacology, and some companies support training in collaboration with the NHS.

## Appendix 2: Challenge agents

### Some examples of challenge agents and their uses

Challenge agent	Activity	Route of administration and use
allergens	allergy	skin prick or inhalation (asthma only); to assess anti-allergy activity
AMP	transmitter release	inhalation; to assess anti-allergy effect
capsaicin	villanoid receptor agonist	inhalation; stimulates cough reflex
histamine	H <sup>1</sup> - & H <sup>2</sup> -agonist	skin prick; to assess anti-allergy activity
hyoscine	muscarinic antagonist	sc; dementia model
ipecac	causes nausea and vomiting	oral; to assess anti-emetic activity via 5-HT <sub>3</sub> or NK1 receptor inhibition
isoprenaline	β-receptor agonist	iv; to assess blocking activity
norepinephrine	α- & β-receptor agonist	iv; to assess blocking activity
methacholine	muscarinic receptor agonist	inhalation; to assess airway responsiveness
substance P	NK-receptor agonist	skin prick; to assess NK blocking activity
serotonin	5-HT agonist	iv, to assess blocking activity
tyramine	norepinephrine release	oral or iv; to assess MAO-B selectivity
P450 probes*	P450 phenotypes	oral; to assess potential for interactions with established medicines

### Examples of radioactive isotopes for PET or SPECT scans

PET		SPECT	
radioisotope	half-life (min)	radioisotope	half-life (h)
<sup>82</sup> Rb	1	<sup>99m</sup> Tc	6
<sup>15</sup> O	2	<sup>123</sup> I	13
<sup>13</sup> N	10	<sup>111</sup> In	67
<sup>11</sup> C	20	<sup>201</sup> Tl	73
<sup>68</sup> Ga	68	<sup>133</sup> Xe	126
<sup>18</sup> F	111		

\* There are various probes, including 'cocktails' to assess the activity of cytochrome P450 enzymes 1A2, 3A4, 2C9, 2C19, 2D6 and 2E1, and N-acetyltransferase-2.

## Appendix 3: Abbreviations

**ABPI** - Association of the British Pharmaceutical Industry

**AHPPI** - Association for Human Pharmacology in the Pharmaceutical Industry

**ALS** - Advanced life support

**AMS** - accelerator mass spectrometry

**AREC** - Association of Research Ethics Committees

**ARSAC** - Administration of Radioactive Substances Advisory Committee

**BIA** - BioIndustry Association

**BLS** - Basic life support

**CAP** - College of American Pathologists

**CHM** - Commission on Human Medicines

**COSHH** - Control of Substances Hazardous to Health

**CPA** - College of Pathology (UK) Accreditation

**CPD** - Continuing Professional Development

**CRF** - case report form

**CRO** - contract research organisation

**CTA** - Clinical Trial Authorisation

**DCPSA** - Diploma in Clinical Pharmacology of the Society of Apothecaries

**DHP** - Diploma in Human Pharmacology

**Dip Pharm Med** - Diploma in Pharmaceutical Medicine

**DNA** - deoxyribonucleic acid

**ECG** - Electrocardiogram

**EEA** - European Economic Area

**EMA** - European Agency for the Evaluation of Medicinal Products

**ESG** - Expert Scientific Group

**EU** - European Union

**EudraCT** - European Union database of clinical trials

**FDA** - Food and Drug Administration of the USA

**FFPM** - Fellow of the Faculty of Pharmaceutical Medicine

**FIBMS** - Fellow of the Institute of Biomedical Science

**FIH** - First In Human

**FRCA** - Fellow of the Royal College of Anaesthetists

**FRCP** - Fellow of the Royal College of Physicians

**GAfREC** - Governance Arrangements for NHS Research Ethics Committees

**GCP** - good clinical practice

**GLP** - good laboratory practice

**GMC** - General Medical Council

**GMM** - genetically modified micro-organisms

**GMP** - good manufacturing practice

**GP** - General Practitioner (primary care physician or equivalent)

**GTAC** - Gene Therapy Advisory Committee

**HIV** - human immunodeficiency virus

**HRA** - NHS Health Research Authority

**HSE** - Health and Safety Executive

**ICH** - International Conference on Harmonisation

**ILS** - Immediate life support

**ISO** - International Standards Organisation

**IMP** - investigational medicinal product

**MABEL** - minimal anticipated biological effect level

**MD** - Doctorate in Medicine

**MFPM** - Member of the Faculty of Pharmaceutical Medicine

**MHRA** - Medicines and Healthcare products Regulatory Agency

**MIA (IMP)** - Manufacturer's Authorisation for an IMP

**MRCP** - Member of the Royal College of Physicians

**mSv** - milliSievert

**NCE** - new chemical entity

**NEQAS** - National External Quality Assessment Service

**NHS** - National Health Service

**NOAEL** - no-observed-adverse-effect level



**PET** - positron emission tomography

**PhD** - Doctorate in Philosophy

**PI** - Principal Investigator

**PML** - progressive multifocal leukoencephalopathy

**PMST** - Pharmaceutical Medicine Speciality Training

**QP** - qualified person

**RCP** - Royal College of Physicians

**REC** - research ethics committee

**RES** - Research Ethics Service

**SAE** - serious adverse event

**SI** - statutory instrument

**SOP** - standard operating procedure

**SPECT** - single photon emission computed tomography

**SUSAR** - suspected unexpected serious adverse reaction

**TOPS** - The Over-Volunteering Prevention System

**UKECA** - United Kingdom Ethics Committee Authority

## Appendix 4: Glossary of terms

**Accelerator mass spectrometry (AMS)** – an extremely sensitive and accurate method of analysing a very small dose – a microdose – of an IMP labelled with an isotope (<sup>14</sup>C).

**Accreditation** - recognition that a trial-related function meets an official quality standard. Examples are accreditation of a quality system by ISO 9001, a pathology laboratory by a College of Pathology, a Phase I unit by MHRA, and a REC by RES (formerly COREC).

**Administration of Radioactive Substances Advisory Committee (ARSAC)** - decides if the amount of radioactivity subjects receive in a clinical trial is within acceptable limits.

**Adverse event (AE)** - an unwanted clinical symptom, sign or disease, or an abnormal laboratory finding, that is related in time to, but is not necessarily caused by, the administration of an IMP to a subject in a clinical trial.

**Agonist** – binds to a cell receptor and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance.

**Algorithm** – procedure for making a series of choices among alternative decisions to reach an outcome.

**Anaphylactic reaction** - an allergic reaction that is life-threatening.

**Antigen** – a substance which when introduced into the body stimulates the immune system to make a specific immune response, such as production of an antibody that binds to the antigen. An antigen may cause an allergic reaction.

**Appraisal** - a review of a person's performance and development needs.

**Association of the British Pharmaceutical Industry (ABPI)** – a trade association of pharmaceutical, biotechnology, research and development, or associated companies with either their main or subsidiary premises in the UK.

**Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI)** - a group of people who are involved in commercial Phase I trials and hold biannual symposia to educate members.

**Audit** - a systematic and independent review of trial-related activities and documents, to find out if the activities were carried out, and if the data were recorded, analysed, and accurately reported, according to the protocol, SOP, GCP, GMP and regulatory requirements.

**Audit certificate** - written evidence that a trial-related function has been audited.

**Audit report** - an auditor's written report of his or her findings.

**Audit trail** - documentation of events at each stage of a trial that allows an auditor to trace the source of the data, track changes, and assess if the data are genuine.

**Batch** - a defined amount of starting material, packaging material or IMP that is prepared in one process or a series of processes and is expected to be uniform within specified limits.

**Batch release** - the process of signing off a batch of IMP by a qualified person (QP).

**Bioavailability** - a measure of how well a medicine is absorbed by the body.

**Bioequivalence** - two medicines are bioequivalent if their bioavailability does not differ significantly when they are used in a trial at the same dose and under similar conditions.

**Biological investigational medicinal products** - potential new medicines, such as proteins, cytokines, monoclonal antibodies, genetically-modified micro-organisms and gene therapy, resulting from advances in cell biology and in biotechnology.

**Biomarker** - a laboratory or clinical measure of the body's response to an IMP that might indicate that the IMP is working. When a biomarker can replace a clinical endpoint it is called a surrogate endpoint.

**Biotechnology** - the application of the biological sciences, especially genetics, to technological or industrial uses.

**BioIndustry Association (BIA)** – a trade association for the UK bioscience sector.

**Bivalent antibody** – antibody with two binding sites.

**Blinding** - a procedure in which one or more of the parties to a trial do not know which IMP (active, placebo or comparator) is allocated to which trial subject.

**Calibration** - demonstrating that an instrument or device gives results within specified limits by comparing them with the results obtained with a standard over a range of measurements.

**Case report form (CRF)** - a printed, optical, or electronic document designed to record all of the information that is required by the clinical trial protocol, and is to be reported to the sponsor, for each trial subject.

**Certificate of analysis** - a document of the identity, purity and strength of an IMP.

**Chief investigator** - leads a group of principal investigators.

**Clinical (human) pharmacology** - the scientific basis of Phase I trials.

**Clinical Trial Authorisation (CTA)** - sponsors must obtain a CTA from the MHRA before they can start a trial of an IMP.

**Clinical trial (study)** - tests the safety and activities of an IMP in humans.

**Clinical trial (study) report** - includes all the results of a trial and an analysis and clinical interpretation of them.

**Comparator** - a marketed medicine, a placebo, or another preparation of an IMP used for comparison in a trial.

**Complement system** – many small plasma proteins that work together to clear pathogens, such as bacteria, and promote healing.

**Compliance** - meeting the relevant requirements for a trial-related function.

**Confidentiality** - making sure that only authorised people see a sponsor's proprietary information or know a trial subject's identity.

**Concentration-response curve** – relationship between concentration of the IMP in blood or tissues and its effect.

**Continuing Professional Development (CPD)** - process by which physicians keep up-to-date, develop new skills and maintain a high standard of professional practice.

**Contract** - a written, dated and signed agreement among the parties to a trial, such as the sponsor, investigator and CRO, that sets out the duties and responsibilities, including financial, of each party (the protocol can be the basis of the contract).

**Contract research organisation (CRO)** - a commercial, academic or other type of organisation that may carry out the sponsor's trial-related duties and functions.

**Control of Substances Hazardous to Health (COSHH)** - regulations to protect workers against any substance in the workplace that might damage their health.

**Curriculum vitae (CV)** - written details of the researchers' qualifications and experience that enable sponsors, MHRA or REC to assess the eligibility of the researchers to do a trial.

**Cyclotron** - produces radioactive isotopes of short half-life for research or diagnostic imaging.

**Cytokine** - small proteins produced by cells, mainly white blood cells, in response to an immune stimulus. They mediate and regulate immunity and inflammation.

**Cytokine storm** - uncontrolled release of cytokines which react with immune cells. A cytokine storm damages tissues and organs, which may be fatal.

**Data Protection Act** - legislation to give people the right of control of personal information that is held about them.

**Declaration of Helsinki** - guidelines of the World Medical Association that protect the rights, safety and well-being of subjects who take part in clinical trials, and are revised every four years – Directive 2001/20/EC is based on the 1996 version.

**Delayed hypersensitivity reaction** – a harmful immune response caused by re-exposure to a protein to which the body has become sensitive as a result of a previous exposure.

**Deoxyribonucleic acid (DNA)** - the substance in cells that carries the genetic code for the individual.

**Diploma in Pharmaceutical Medicine (Dip Pharm Med)** - a qualification in pharmaceutical medicine awarded by the Faculty of Pharmaceutical Medicine.

**Diploma in Human Pharmacology (DHP)** - a qualification for principal investigators for Phase I trials to be awarded by the Faculty of Pharmaceutical Medicine.

**Direct access** - permission to examine, analyse, verify and reproduce the relevant records and reports of a clinical trial.

**Documentation** - the process of creating records, in a written, magnetic, optical or other form, that describes the methods and conduct of the study, factors affecting it, and the action taken. Records include the protocol and any amendments, copies of submissions and approvals from the MHRA and REC, curricula vitae, information and consent forms, monitor's reports, audit certificates, relevant letters, reference ranges, raw data, completed CRF and the final study report.

**Dose** - the amount of an IMP given to the trial subject on one or more occasions (single- or multiple-dose). A dose may be one or more tablets, capsules, injections or other form of the IMP.

**Dose-response curve** – relationship between doses of an IMP and their effect.

**Efficacy** - whether an IMP is effective.

**Endoscopy** – looking into parts of the body – such as the stomach and windpipes – with an endoscope, a thin fibre-optic telescope with a light at the end.

**Essential documents** - documents that are kept in the trial master file and enable the sponsor or MHRA to assess if a trial was carried out properly and to judge the quality of the data produced.

**European Agency for the Evaluation of Medicinal Products (EMA)** - coordinates the regulatory authorities, such as the MHRA, of all the EU countries.

**European Commission (EC)** - an institution in Brussels that drafts proposals for EU legislation and does the day-to-day work of running the EU.

**European database of clinical trials (EudraCT)** - a database in which all EU clinical trials must be registered.

**European Economic Area (EEA)** - the EU plus Iceland, Norway and Lichtenstein.

**European Union (EU)** - a group of European countries with common policies.

**Exclusion criteria** - reasons for excluding a subject from a trial, such as taking another medicine, having an illness or having out-of-range laboratory results.

**Expert Advisory Group of the Commission on Human Medicines** – The Commission on Human Medicines advises the Government and the MHRA about medicinal products. Expert Advisory Groups – such as the one for higher risk biological IMP – support the Commission.

**Expert Scientific Group (ESG) Report on Phase I Clinical Trials** - report of an enquiry into the First-in-Human trial of TGN1412.

**Faculty of Pharmaceutical Medicine** - a section of the Royal College of Physicians that sets and maintains standards in pharmaceutical medicine through Pharmaceutical Medicine Specialty Training.

**Fc receptor** – protein found on the surface of certain white blood cells that contribute to the protective function of the immune system.

**Finished product** - an IMP that has undergone all stages of manufacture, including packaging and labelling in its final container.

**First-in-Human clinical trial** - a clinical trial in which a potential new medicine is given to humans for the very first time.

**General Medical Council (GMC)** - registers and regulates UK physicians.

**Genes** - a biological unit of heredity - a sequence of DNA that codes for one protein. The human genome has about 70,000 genes.

**Gene therapy** - the deliberate introduction of genetic material into human somatic cells for therapeutic, prophylactic or diagnostic purposes.

**Gene Therapy Advisory Committee (GTAC)** - reviews proposals to conduct gene therapy research and advises about gene therapy.

**Genetic testing** - to detect the presence or absence of, or variation in, a particular gene using a DNA, biochemical or other test. The metabolism of many medicines is affected by genetic differences in enzymes.

**Genetically modified micro-organisms (GMM)** - micro-organisms that have had their genetic material altered by artificial means.

**Good clinical practice (GCP)** - an international ethical and scientific quality standard for designing, conducting, recording, monitoring and reporting studies that involve human subjects. GCP ensures that the rights, safety and well-being of the trial subjects are protected, and that the trial data are credible and accurate.

**Good laboratory practice (GLP)** - a set of principles for planning, performing, monitoring, reporting and archiving laboratory studies.

**Good manufacturing practice (GMP)** - a set of principles which ensures that medicinal products are produced and controlled to the quality standards appropriate to their intended use.

**Governance Arrangements for NHS Research Ethics Committees (GAfREC)** - guidelines issued by the Research Ethics Service (RES) that all REC must follow.

**Half-life** - time for the concentration of an IMP or medicine to halve in the body.

**Health and Safety Executive (HSE)** - responsible for enforcing regulations that ensure the health and safety of staff and visitors in the workplace.

**Health Research Authority (HRA)** – Regulatory body in England to protect and promote the interests of patients and the public in health and social care research. The appointing authority for RECs in England.

**HRA Approval** – Required for all research taking place in the NHS.

**Hepatitis viruses B and C (HVB and HVC)** - viruses that are transmitted by blood or blood products and cause liver disease.

**Higher risk agent** - an IMP that the ESG Report deemed more likely to cause harm than other IMPs when tested for the first time in humans: biological molecules with novel mechanisms of action; new agents with a highly species-specific action; and new agents directed towards immune system targets.

**Human immunodeficiency virus (HIV)** - the virus that causes AIDS.

**Human Tissue Act** – legislation to regulate the removal, storage and use of human organs and tissues.

**Imaging** - taking a picture of part of the body using a special detector and a computer.

**Immune response** - a white blood cell, antibody or cytokine response to an antigen, infection or some other stimulus.

**Importing** - bringing an IMP into the UK from a third country, such as the USA.

**Inclusion criteria** - conditions that must be met if a subject is to join a trial.

**Indemnity** - a guarantee inserted in the protocol, contract or subject information leaflet that the sponsor will compensate a trial subject who is harmed by taking part in a clinical trial.

**Informed consent** - a process by which subjects voluntarily confirm their willingness to take part in a trial after having been fully informed about it. Informed consent is documented by means of a written, signed and dated consent form.

**Inspection** - the act by a regulatory authority of reviewing the documents, facilities, records, and any other resources related to the clinical trial and that may be located at the trial site, at the facilities of the sponsor or CRO or at other establishments.

**Insurance** - provides cover for the sponsor or investigator in the event of a claim for damages by a trial subject.

**International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)** - ICH version of GCP, which provides a unified standard for the EU, Japan and USA to facilitate the mutual acceptance of clinical data by the regulatory authorities in those countries.

**Investigational medicinal product (IMP)** - a potential new medicine, a placebo or a comparator. Includes a marketed product when used or assembled in a way different from the approved form, or when used for an unapproved indication or to gain further information about an approved use.

**Investigational medicinal product dossier (IMP dossier)** - gives information about the quality, manufacture and control of the IMP, including any comparator or placebo, and pre-clinical data and any clinical data.

**Investigator** - a researcher who carries out a clinical trial. A principal investigator leads a team of researchers. A chief investigator leads a group of principal investigators. In some units, the chief investigator and the principal investigator may be the same person.

**Investigator's brochure** - contains all the information and evidence, including non-clinical and any clinical data on the IMP, that support the proposed trial.

***in vitro*** – outside the body, such as in a test tube (the opposite of *in vivo*).

***in vivo*** – in the living body.

**International Standards Organisation (ISO)** – responsible for the ISO 9000 and other quality standards.

**Isotope** - one of two or more atoms having the same atomic number but a different atomic mass. Isotopes such as <sup>14</sup>C and <sup>3</sup>H are used as tracers in medical tests.

**Ligand** – a molecule that binds to a protein or receptor.

**Manufacture** - any process carried out in the course of making an IMP, except dissolving or dispersing it in, or diluting or mixing it with, another substance used as a vehicle to administer the IMP.

**Manufacturer's Authorisation for IMP [MIA (IMP)]** - a licence, granted by the MHRA, to import or manufacture an IMP.

**Marketing Authorisation** - a licence, granted by the MHRA, that enables a manufacturer to sell a medicinal product so that doctors can prescribe it for patients.

**Medicines and Healthcare products Regulatory Agency (MHRA)** - a body required by law to assess the safety, quality and efficacy of medicinal products and devices, and to enforce GCP, GMP and GLP.

**Metabolism** - the breakdown of substances, including IMP, by the body.

**Microdose** – less than one hundredth of the predicted pharmacological dose but not exceeding 100 micrograms.

**Monitoring** - the act of overseeing the progress of a clinical trial, to ensure that it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, GMP, GLP, and any regulatory requirements.

**Monoclonal antibodies** - identical antibodies cloned from a single cell by a biotechnology method. They target a specific cell or protein in the body. Several monoclonal antibodies are in clinical use and many more are under development.

**Mutual Recognition Agreement (MRA)** - an agreement between the EU and an exporting third country to allow an IMP to be imported into the EU.

**Needlestick (sharps) injury** - an injury caused by penetration of the skin by a needle or other sharp object, which may result in infection with blood-borne viruses such as hepatitis B and C, and HIV.

**New chemical entities (NCE)** - potential new medicines that are derived from chemical substances. They are sometimes referred to as small molecules.

**No-observed-adverse-effect dose level (NOAEL)** - the highest IMP dose level that is free of toxic effects in animal toxicology studies.

**Non Investigational Medicinal Product (NIMP)** – A NIMP is defined as a medicinal product that falls within Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMP as defined in Article 2(d) of Directive 2002/20/EC; that is a medicinal product which may be taken by subjects during a trial but is not classed as an IMP.

**Nuclear medicine** - use of radioactive isotopes for diagnosing or treating disease.

**Nursing and Midwifery Council (NMC)** - the organisation that controls nursing in the UK. All nurses must be registered with the NMC to carry out nursing duties.

**Pharmaceutical medicine** - the discipline concerned with the discovery, development, assessment, registration, monitoring and medical marketing of medicines.

**Pharmaceutical Medicine Specialty Training** - consists of seven advanced training modules in pharmaceutical medicine, of which clinical pharmacology is one, leading to the award of the Certificate of Completion of Training (CCT) by the Royal Colleges of Physicians.

**Pharmacodynamics** - the study of the effects of an IMP on the body and the mechanisms by which it acts (what the IMP does to the subject).

**Pharmacokinetics** - the study of the time course of the concentrations of an IMP and related substances in the blood and other parts of the body (what the subject does to the IMP). The concentrations depend on the processes of absorption (from the site of administration of the IMP), distribution in the tissues, metabolism (breakdown) and excretion (getting rid of it).

**Pharmacology** - information about the activities of an IMP in animals or humans.



**Pharmacovigilance** - collecting information about the safety of an IMP.

**Phase I** - trials of an IMP in subjects, either healthy subjects or patients, who will not benefit from the IMP.

**Phase II** - early trials of an IMP in subjects with the target disease who are expected to benefit from the IMP.

**Phase III** - late trials of an IMP in many subjects with the target disease who are expected to benefit from the IMP.

**Phase IV** - post-marketing trials of a medicine to compare it with other treatments.

**Photon** - a quantum of electromagnetic radiation.

**Placebo** - a preparation that looks and may taste like the IMP that is being tested but contains no active substance (a dummy medicine).

**Positron** - a positive charge emitted from the nucleus of a radioactive isotope.

**Positron emission tomography (PET)** - a scanner gives a picture of the radioactivity taken up by a 'slice' of an organ, such as the brain, after administration of a radioactive isotope. PET measures metabolism or locates chemical transmitters.

**Pre-clinical studies** - studies in laboratory animals *in vivo* or in tissues, cells, components of cells or biological fluids of laboratory animals or humans *in vitro* before the start of Phase I trials. Also called non-clinical studies.

**Principal investigator (PI)** - leads a team of investigators (researchers).

**Progressive multifocal leukoencephalopathy (PML)** - a rare and fatal infection of the brain and spinal cord caused by reactivation of JC polyoma virus (a normally harmless virus that 80% of people carry) in patients with severely impaired immunity.

**Protocol** - a document that describes how a clinical trial will be done and includes information about the trial, such as the background, reasons, aims, ethics, design, methods, records, data management and statistics.

**Protocol amendment** - a document that describes a change to a protocol.

**Publication policy** - a policy agreed between the investigator(s) and sponsor for publishing the results of a trial in a scientific or medical journal.

**Pulse oximetry** - a non-invasive and painless way to measure, from the surface of the skin, the amount of oxygen in arterial blood.

**Quality assurance (QA)** - all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, recorded and reported in compliance with GCP and with MHRA regulations.

**Quality control (QC)** - checking the quality of trial-related activities.

**Qualified person (QP)** - someone who ensures that each batch of an IMP that is made within the EU meets the requirements of GMP and that each batch of an IMP made outside the EU meets GMP requirements at least equivalent to those in the EU.

**Quarantine** - the status of materials, product or information that is isolated pending a decision on its approval or rejection.

**Radioactive isotope** - an unstable form of an element that breaks up into other elements and in so doing gives out radiation that can be measured.

**Radiolabel** - technique of incorporating a radioactive isotope into a molecule.

**Radiopharmaceutical product** - a product that includes a radioactive isotope.

**Randomisation** - the process of allocating trial subjects to IMP (active, placebo or comparator) by chance, so as to reduce bias.

**Receptor** - a structure on the surface of a cell (or inside the cell) that selectively receives and binds a specific substance.

**Regulatory (competent) authorities** - bodies such as the MHRA that review submitted clinical data and conduct inspections.

**Reproductive toxicology** - a series of toxicity tests in animals to assess the risk of giving an IMP to a fertile woman or man, or a woman who is pregnant.

**Research Ethics Committee (REC)** - an independent group of medical and scientific professionals and members of the public, with no financial interests or affiliations with the sponsor or researchers, who give an opinion on the ethics of a trial.

**Research Ethics Service (RES)** - The functions of RECs which operate within the Research Ethics Service are set out in the RES Standard Operating Procedures



**Rescue medication** - treatment given to a subject to relieve a problem brought about by taking part in a clinical trial.

**Resuscitation Council (UK)** – provides education and reference materials to healthcare professionals and the general public in the most effective methods of resuscitation.

**Risk** – potential for harm.

**Scintillation counter** - a machine for measuring radiation, that counts light flashes emitted from a detector substance exposed to radiation.

**Serious adverse event (SAE) or serious adverse drug reaction (serious ADR)** - any untoward medical event that at any dose of a medicinal product:

- results in death
- is life-threatening
- requires a stay in hospital or prolongs an existing stay in hospital
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly or birth defect.

**Shipping (dispatch)** - packing and sending trial-related material somewhere.

**Sievert** – a unit of radiation exposure. The average person in the UK receives about 2.5 milliSievert of 'background' radiation annually from the environment. A chest X-ray represents about 10 days of 'background' radiation.

**Signature** - a distinct record (initials, or full handwritten or electronic signature) of the person who was responsible for a particular action or review.

**Single photon emission computed tomography (SPECT)**

- similar to positron emission tomography but uses an isotope with a longer half-life (hours rather than minutes) that does not have to be made by a cyclotron machine.

**Single photon emitters** - radioactive isotopes that mainly emit gamma or X-rays.

**Small molecules** - see new chemical entities.

**Somatic cells** - cells other than egg or sperm cells.

**Source data** - all information in original records, and certified copies of original records, of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are found in source documents.

**Source documents** - original or certified copies of documents, data and records such as charts, laboratory notes, memoranda, diaries, checklists, dispensing records, printed output from instruments, and records kept at the pharmacy, laboratories and other departments involved in the trial.

**Sponsor** - an individual, company, institution or organisation that is responsible for the initiation, management and/or financing of a clinical trial.

**Standard operating procedures (SOP)** - detailed, written instructions to ensure that trial-related procedures are done in the approved way by everybody.

**Statutory instrument (SI)** – a power delegated by Parliament. Parliament can delegate its power to make and amend law to a person or organisation. A statutory instrument is one of these powers and is used by government ministers to amend legislation.

**Sterility** - the absence of living organisms.

**Subject identification code** - a unique identifier assigned by the investigator to each trial subject and used instead of the subject's name when the investigator reports adverse events and/or other trial-related data.

**Subrogation** – substituting one person or organisation for another, including all rights and responsibilities.

**Suspected unexpected serious adverse (drug) reaction (SUSAR)** - a serious adverse event considered by the investigator or sponsor to be possibly or probably related to the IMP under test and for which the nature and/or severity differs from the information in the investigator's brochure.

**Target disease** - the disease for which a potential new medicine is being developed.

**Technical agreement** - agreement between sponsor and investigator for the IMP.

**TGN1412** - a monoclonal antibody that differs from those in clinical use in that it activates rather than blocks the body's immune response – so it is called a 'superagonist'.

**Third country** - countries, such as Japan and the USA, that are members neither of the EU nor the EEA.

**TOPS (The Overvolunteering Prevention System)** - an internet-based system to prevent subjects from taking part in Phase I trials too often.

## Appendix 5: Consultation responses

Feedback from the following organisations were received, either on the 2007, 2012 or this current 2018 edition. The list is not exhaustive and many more organisations were invited to comment.

ABPI member companies

ABPI Expert Networks – in particular the Experimental Medicine Expert Network and Legal Expert Network.

Authorising Authority for Phase I Ethics Committees (AAPEC)

Cancer Research UK

Clinical Contract Research Association (CCRA) members

Department of Health and Social Care (DHSC)

Independent Ethics Committees for Medical Research (Edinburgh, Plymouth)

Good Clinical Practice (GCP) Inspectorate, MHRA

Medicines and Healthcare products Regulatory Authority (MHRA)

Medical Research Council (MRC)

NHS Health Research Authority (HRA)

Research Ethics Service (RES)

Royal College of Physicians (RCP)

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